PROTOCOL

Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma : PACKMaN

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This protocol has regard for current HRA guidance and content.

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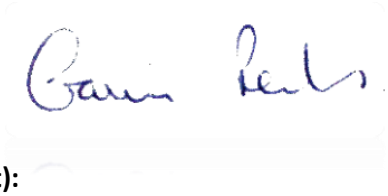
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/199828) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

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

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

Chief Investigator:
Signature:  **Date: 5 December 2023**

Name (please print):
Gavin Perkins

Co-Chief Investigator:
Signature:  Date: 17/11/2023

Name (please print):

Michael Smyth

Statistician:
Signature: Date:

 20/11/2023

Name (please print): Ranjit Lall

CONTACT NAMES AND NUMBERS

Role	Name, address, telephone
Sponsor:	Carole Harris Research and Impact Services University House University of Warwick Coventry CV4 8UW Tel: 02476 575732
Chief Investigator:	Gavin Perkins Professor Warwick Clinical Trials Unit Gibbet Hill Campus University of Warwick Coventry CV4 7AL Tel: 02476 575288 Email: G.D.perkins@warwick.ac.uk
Co-Chief Investigator:	Michael Smyth Dr Warwick Clinical Trials Unit Gibbet Hill Campus University of Warwick Coventry CV4 7AL Tel: 02476 528039 Email: m.a.smyth@warwick.ac.uk

Role	Name, address, telephone
Trial Manager:	Hannah Noordali Dr Warwick Clinical Trials Unit Gibbet Hill Campus University of Warwick Coventry CV4 7AL Tel: 02476 150478 Email: packman@warwick.ac.uk
Senior Project Manager	Kath Starr Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: Email: kath.star@warwick.ac.uk
Co-investigators:	Joyce Yeung Dr Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 02476 573357 Email: J.Yeung.4@warwick.ac.uk

Role	Name, address, telephone
Co-investigators:	Ranjit Lall Professor Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 02476 574649 Email: R.Lall@warwick.ac.uk
Co-investigators:	Gordon Fuller Dr School of Health and Related Research (ScHARR) University of Sheffield Regent Court 30 Regent Street Sheffield S1 4DA Tel: 0114 222 4389 Email: g.fuller@sheffield.ac.uk
Co-investigators:	Stavros Petrou Professor Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Tel: 01865 289503 Email: stavros.petrou@phc.ox.ac.uk
Co-investigators:	Alison Walker Dr Trust Headquarters Millennium Point Waterfront Business Park Waterfront Way Brierley Hill West Midlands DY5 1LX Tel: 01384 246442 Email: alison.walker@wmas.nhs.uk

Role	Name, address, telephone
Co-investigators:	Julian Mark Dr Yorkshire Ambulance Service NHS Trust Springhill 2 Brindley Way Wakefield 41 Industrial Estate Wakefield WF2 0XQ Email: j.mark@nhs.net
Co-investigators/PPI:	Duncan Buckley Mr
Statistician:	Ranjit Lall Professor Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 02476 574649 Email: r.lall@warwick.ac.uk
Health Economist:	Stavros Petrou Professor Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Tel: 01865 289503 Email: stavros.petrou@phc.ox.ac.uk
Specialist Collaborator(s):	MODEPHARMA Limited 114 Barnfield Wood Road Beckenham BR3 6SX Tel: 0207 043 2442 Email: ogupta@modepharma.com
Specialist Collaborator(s):	Huddersfield Pharmacy Specials (HPS) Gate 2 Acre Mill School Street West Lindley Huddersfield HD3 3ET

Role	Name, address, telephone
Trial Steering Committee:	Chair: Dr Fionna Moore South East Coast Ambulance Service NHS Foundation Trust Nexus House 4 Gatwick Road Crawley Sussex RH10 9BG Email: Fionnapmoore@gmail.com Tim Edwards London Ambulance Service NHS Trust Email: timothy.edwards@lond-amb.nhs.uk Andy Collen South East Coast Ambulance Service NHS Foundation Trust Email: andy.collen@secamb.nhs.uk Caroline Leech University Hospitals Coventry and Warwickshire NHS Trust Email: caroline.leech@uhcw.nhs.uk Jonathan Bishop University Hospitals Birmingham NHS Foundation Trust Email: j.bishop.1@bham.ac.uk Claire Hulme University of Exeter Email: C.T.Hulme@exeter.ac.uk Sarah Markham (Patient and Public Representative) Claire Jowett (Patient and Public Representative)

Role	Name, address, telephone
Data Monitoring Committee:	Chair: Prof. Siobhan Creanor College House University of Exeter St. Luke's Campus Heavitree Road Exeter EX1 2LU Email: E.S.Creanor@exeter.ac.uk Prof. Julia Williams University of Hertfordshire Email: j.williams@herts.ac.uk Dr. Charlotte Small Wye Valley NHS Trust Email: charlottelucy.small@nhs.net

For general queries and supply of trial materials please contact the coordinating centre:

Warwick Clinical Trials Unit (WCTU)
The University of Warwick
Gibbet Hill Road
Coventry
CV4 7AL
Tel: 02476 574880
Email: PACKMaN@warwick.ac.uk

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TRIAL SUMMARY

Trial Title	Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma : PACKMaN
Hypothesis	Ketamine is superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics.
Trial Design	Multi-centre, pragmatic, randomised controlled, blinded, trial, with economic evaluation and internal pilot.
Trial Participants	Adult patients (age ≥16 years) with severe pain following acute traumatic injury
Setting	West Midlands and Yorkshire NHS Ambulance Services
Inclusion criteria	1. Age ≥16 2. Patient reports a pain score ≥7/10 on a 0-10 numeric rating scale following acute traumatic injury 3. Intravenous (IV) or intraosseous (IO) access obtained 4. Determined by a paramedic to require IV morphine or equivalent
Exclusion criteria	1. Known or suspected pregnancy 2. Unable to articulate severity of pain using the 0-10 numeric rating scale 3. Lack of capacity due to a reason other than pain 4. IV/IO ketamine or opioid analgesia immediately prior to randomisation 5. Known contraindication to ketamine or morphine as per the SmPC 6. Patient declines participation 7. Known prisoner
Sample size	446 (223 each arm with 1:1 randomisation)
Interventions being assessed	Pre-hospital ketamine hydrochloride (0.15mg / kg) or morphine sulphate (0.10mg / kg)
Measurement of outcomes and costs	**Primary Outcome** • Effectiveness of pain relief from randomisation to arrival at hospital as measured by Sum of Pain Intensity Difference (SPID) score (using a 0-10 numerical rating scale) **Secondary Outcomes** • Effectiveness of pain relief and overall patient experience from randomisation to arrival at hospital • Incidence of side effects and adverse events • Resource use • Longer term outcomes
Follow-up Duration	6 months from randomisation
Trial Period	01/01/2020 – 31/05/2024

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
AR	Adverse Reaction
BNF	British National Formulary
BPI-SF	Brief Pain Inventory (Short Form)
CCP	Critical Care Paramedics
CI	Chief Investigator
CNS	Central Nervous System
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Developmental Safety Update Report
ED	Emergency Department
EOC	Emergency Operations Centre
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
HRQL	Health-Related Quality of Life
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IO	Intraosseous
IRAS	Integrated Research Application System
IV	Intravenous
JRCALC	Joint Royal College Ambulance Liaison Committee
LR	Legal representative
MHRA	Medicines and Healthcare products Regulatory Agency

NRS	Numeric Rating Scale
PI	Principal Investigator
PPI	Patient & Public Involvement
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
QP	Qualified Person
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SMUR	Emergency Mobile Resuscitation Unit
SPID	Sum of Pain Intensity Difference
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARN	The Trauma Audit and Research Network
TOTPAR	Total Pain Relief Score
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

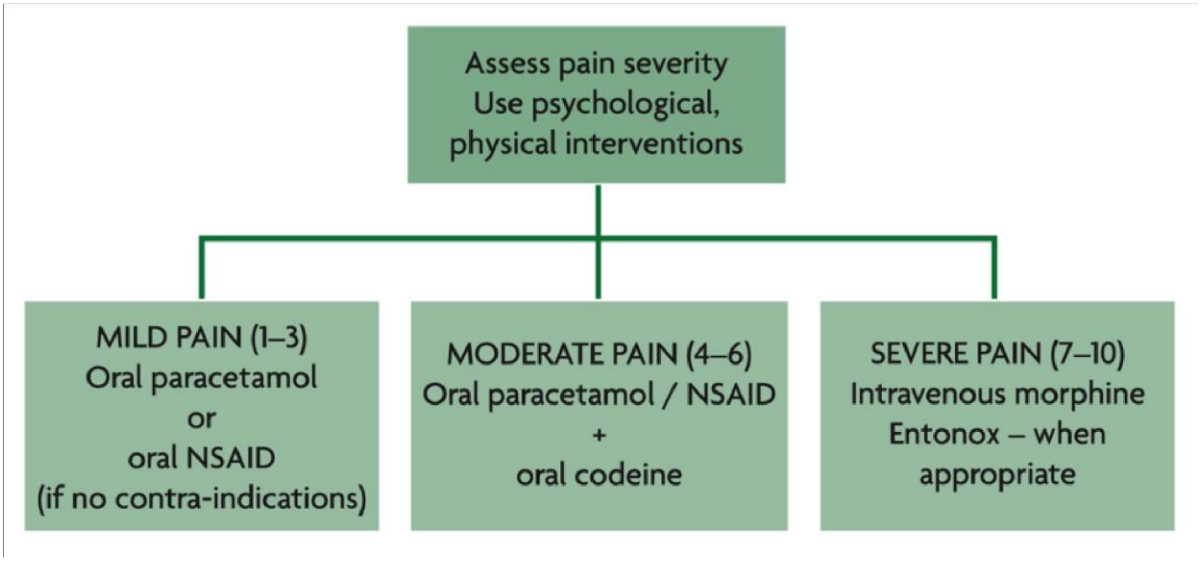
1.1 Epidemiology and burden of the condition

Pain after traumatic injury is common, yet few patients receive adequate pain relief. NHS Paramedics have a limited formulary to treat severe pain. Ketamine may be an ideal prehospital analgesic agent due to its rapid onset of action, superior analgesic properties and haemodynamic profile. NICE has identified the need for a pragmatic, randomised trial to determine the clinical and cost effectiveness of ketamine against standard care (morphine).

At least 70% of Ambulance calls involve patients experiencing pain.[1] Observational studies suggest that current treatments leave many patients with inadequate pain relief in the prehospital environment.[2-6] The effective management of acute pain is important for humanitarian reasons, for improving patient experience and reducing adverse long term outcomes. In 2004 the World Health Organisation declared that effective management of pain is a universal human right. Poorly managed acute pain is associated with increased chronic pain. Studies indicate chronic pain is common following trauma with a reported incidence of 15-30%, increasing to 62% in patients suffering major trauma.[7-9] Poorly managed postoperative pain leads to persistent pain in 10-50% of common surgeries, and that pain is severe in about 2-10% of these patients.[10] Military personnel injured in recent conflicts demonstrate a link between acute pain management and depression and post-traumatic stress disorder (PTSD). Early aggressive pain management exerts a protective effect on the development of PTSD (OR 0.47 (95%CI 0.34-0.66) and depression (0.40 (95%CI 0.17 – 0.94) .[11, 12] Provision of early and effective analgesia has the potential to reduce the risk of developing chronic pain and adverse mental health outcomes post trauma which may impact on patient's long term quality of life.[13, 14]

Current approach

The Joint Royal Colleges Ambulance Liaison Committee (JRCALC) produce national clinical guidelines for NHS Ambulance Services. These guidelines suggest a stepwise approach to pain management according to the pain severity and availability of pre-hospital treatments for pain. (see figure 1)



(Figure 1) Approach to prehospital pain management

Trial Rationale

A barrier to effective pain treatment is the limited formulary available to paramedics. The most frequently used drug for moderate to severe pain outside a hospital is morphine.[15] Yet morphine has several side effects (nausea, confusion, dizziness, drowsiness, respiratory depression, arrhythmia) that may limit its use.[16-19] This, and concerns about potential longer term dependence, limits effective use by clinicians.[20] Ketamine is perceived by many to be an ideal prehospital analgesic agent, favoured for its rapid onset of action, effective analgesia, good haemodynamic stability, and preservation of upper airway reflexes.[21] Ketamine has a distinct dose-response gradient in which small doses (<0.5mg/kg) provide an analgesic effect and large doses (>2mg/kg) an anaesthetic effect.[22] It exerts its effect by "disconnecting" the thalamocortical and limbic systems, effectively dissociating the central nervous system (CNS) from outside stimuli (e.g. pain, sight, sound).[23] Ketamine also stimulates the sympathetic nervous system and moderately increases heart rate and blood pressure. Ketamine does not affect respiration; patients breathe spontaneously and maintain airway control.[24] Furthermore, there is evidence to indicate that perioperative ketamine analgesia may prevent hyperalgesia, reducing the risk of developing persistent post-operative pain.[25,26] This suggests the potential for ketamine analgesia to be associated with a lower incidence of chronic pain post trauma. Ketamine also appears to have a wide margin of safety. Serious adverse outcomes have not been reported even though overdoses of 5 to 100 times the intended dose have been inadvertently administered.[27] Due to its rapid onset and favourable side effect profile, ketamine is widely used in ambulance systems around the world.[28-33] In the UK ketamine is currently restricted for use by prehospital doctors and a limited pool of specialist critical care paramedics (CCPs), targeted to the small number of cases needing critical care support.[34,35] The lack of evidence and UK experience with ketamine limits access to a potentially effective treatment.

1.2 Existing knowledge

We conducted a service evaluation of West Midlands Ambulance Service that showed paramedics administered analgesia to 38,400 trauma patients over a 12 month period.[36] Two or more pain scores (0-10 numeric rating scale (NRS)) were documented in 24,081 cases. Amongst these, 7,611 patients receiving morphine, of whom 70.9% (n=5,393) reported moderate or severe pain post analgesia. These data reflect existing studies indicating patients receive inadequate analgesia.[2-4] A survey (n=31) amongst paramedics reported that current analgesic options were inadequate. Five respondents (16.3%) stated they were unable to provide adequate analgesia from the existing formulary at least once every two weeks, while 18 respondents (58.1%) stated this occurred at least once every two months. Respondents felt stronger analgesia should be available. Eleven respondents (35.5%) 'strongly agreed' and 18 respondents (58.1%) 'agreed' that that additional drugs should be available. The majority of respondents favoured a drug with rapid onset and short duration of action, such as ketamine, rather than a slower onset with a longer duration of action, such as morphine.

Existing literature

We searched the literature addressing ketamine analgesia in the prehospital environment and identified five randomised controlled trials (RCTs), [37-41] ten observational studies[21, 22, 29, 34, 42-47] and one systematic review[30] that were relevant. We rated the certainty of evidence using the GRADE framework. Certainty of evidence from RCTs was downgraded from HIGH to VERY LOW due to risk of bias, indirectness and imprecision; whereas the certainty of evidence from observational studies was downgraded from LOW to VERY LOW, also due to risk of bias, indirectness and imprecision.

Ketamine vs placebo: Two RCTs (n=113) compared ketamine or placebo.[37, 40] One trial (intravenous administration by physicians, n=73) reported no difference in pain at 30 minutes but the point

estimate and confidence interval were not reported.[37] The other trial (intranasal by paramedics, n=40) showed reduced pain score in 80% of ketamine group versus 60% of patients administered placebo at 30 minutes.[40] No serious adverse effects were reported in either study.

Morphine alone vs morphine with ketamine: Two RCTs (n=162) compared morphine with morphine plus ketamine.[39,41] In one trial (intravenous administration by physicians, n=65), morphine plus ketamine was more effective than morphine alone (effect size was -2.4 (95%CI -3.2 to -1.6)) and resulted in a quicker reduction of pain intensity (-3.9 (95%CI -4.4 to 3.1) for morphine, -6.5 (95%CI-7.2 to -5.4) for morphine plus ketamine).[39] The other trial (intravenous administration by US paramedics) reported lower pain scores for ketamine and morphine (3.1±1.4) than morphine alone (5.4±1.9).41

Ketamine vs morphine: A single cluster randomised trial in a low-resource setting (intravenous administration by physicians, n=308, Vietnam) showed that ketamine achieved similar analgesic effect to morphine with a mean pain score difference -0.4 (95%CI -0.8 to 0.09). The side effect profile was superior for ketamine with less vomiting observed than for morphine (19% difference, 95% CI 8-22%), although there was a slightly higher rate of hallucinations and agitation (1.5% difference).[38]

Ketamine vs other: Two observational studies totalling 2,034 patients compared ketamine with an opioid other than morphine. Losvik et al compared 888 patients receiving pentazocine with 713 patients receiving ketamine and 275 receiving no analgesia.[47] They did not report on the effectiveness of analgesia, but instead reported on impact on physiologic severity score. Administration of either analgesic was associated with an improvement in respiratory rate score, blood pressure score and change in consciousness score compared with no analgesia. There was no statistically significant difference in any of the aforementioned when comparing patients receiving ketamine or pentazocine.

Bronsky et al compared ketamine with the opioid fentanyl in a propensity matched analysis of 158 patients (79 match pairs).[45] Patients who received ketamine experienced a significantly larger mean decrease in pain after treatment, compared to patients receiving fentanyl (−5.5 (3.1) vs. −2.5 (2.4), $p < 0.001$). A significantly greater proportion of patients receiving ketamine achieved at least a 50% reduction in pain compared to those receiving fentanyl (67% vs. 19%, $p < 0.001$). The authors concluded that ketamine was superior to fentanyl.

Systematic review: A recent systematic review includes two of the RCTs discussed above and four observational studies.[30] None of the included studies address ketamine use by paramedics. The authors report that ketamine, administered in analgesic doses (0.1 to 0.5mg/kg) is as, or more, effective than opioid alone. In addition, ketamine analgesia does not cause greater frequency or severity of side effects compared with other analgesics.

Observational studies and case series: Observational data suggest prehospital ketamine analgesia is as effective or better than morphine and has a low incidence of adverse effects.[29, 34, 43, 46] Although these data are supportive, it is essential to note that studies were conducted in non-UK EMS systems where administration by doctors was common, sample sizes were small and the studies were heterogeneous with significant variation in the types of patients enrolled and dosages administered. A small number of studies indicate ketamine can be safely administered by paramedics, however the existing evidence is insufficient to inform NHS practice.

Ongoing studies: The KETAMORPH study is currently underway in France comparing morphine with ketamine. [48] This trial differs from our proposed design in several respects. KETAMORPH is an open label study with the consequential risks of performance, detection, reporting and attrition bias. The

population being enrolled are heterogeneous as medical and traumatic causes of pain are included whose response to treatment may vary. In addition, ketamine is not ideal for patients with cardiac pain as it increases myocardial workload and may be harmful in this context.[43,49] In NHS practice, morphine is reserved for patients with severe pain (score 7-10 on the numerical rating scale). KETAMORPH by contrast is including patients with moderate to severe pain (pain score 5-10). The dosing regime for morphine in KETAMORPH differs from the dosing regime used in NHS practice (KETAMORPH recommends 2mg aliquots of morphine every 5 minutes, whereas the NHS JRCALC guidelines advocate 2mg aliquots every 1 minutes until 10mg administered). The KETAMORPH regime for morphine will likely lead to less rapid analgesia than current NHS practice. By contrast the initial dose of ketamine is relatively high (30 mg) which may be associated with a higher risk of side effects. KETAMORPH recruitment is limited to specialist, physician led SMUR units. This limits generalisability to the NHS where care is routinely delivered by paramedics. The primary outcome for KETAMORPH is an intermediate outcome of pain relief at 30 minutes as opposed to overall assessment of adequacy of analgesia and other patient reported outcomes proposed in PACKMAN. KETAMORPH is a non-inferiority designed trial. For the NHS to introduce a new treatment, commissioners and healthcare providers would want evidence the treatment is superior to existing treatments. Finally, KETAMORPH does not include an economic evaluation as recommended by NICE. Consequently, the outcome of the KETAMORPH trial will not be able answer the question "is ketamine a superior, cost effective treatment compared to morphine for management of acute severe trauma pain by NHS paramedics?" We continue in dialogue with Dr Emmanuel Montassier who is the chief investigator for the French trial. As highlighted above, recruitment to the KETAMORPH trial is allowed only by the physician led, specialist teams (SMUR). This has limited recruitment as the number of such units is less than general ambulances. The case-mix is narrower than the investigators predicted as the SMUR units are reserved for the most serious cases who often also have multiple other injuries. The investigators developed a new dosing regime, which is different to the SMUR current clinical practice which has reduced clinician's willingness to enrol patients and led to trial protocol deviations. At the time of writing, the KETAMORPH trial has recruited 100 participants (start date November 2017). Dr Montassier remains committed to collaborating and sharing information with the PACKMaN investigators for the benefits of both trials.

1.3 Hypothesis

Ketamine is superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics.

1.4 Need for a trial

Health need: This trial is needed for several reasons. First, pain relief is a fundamental human right.[50-54] Poor management of pain in the prehospital environment is well documented.[2-6] Second, pain adversely impacts physiology and may worsen outcomes. It impairs respiration increasing dead space ventilation, potentially reducing oxygenation.[46] Pain mediated inflammatory response may lead to coagulopathy, organ dysfunction, systemic inflammatory response, lung and brain injury.[55, 56] Third, acute pain impacts functional recovery and contributes to post-injury disability. Long term patient outcomes including chronic pain, anxiety, depression and post traumatic distress disorder have been linked to inadequate early pain management.[5, 6, 55, 56] Fourth, dependence following opioid analgesia is a growing concern.[57-59] Reducing opioid use may have public health benefits.

Expressed need: This proposal is highly relevant to patients and the NHS. This is articulated by (i) current NIHR themed call (ii) the NICE Major trauma guideline (NG39) identifies a need for research comparing morphine with ketamine for first line pain management (iii) The World Health Organisation, pain society and patient groups have declared that analgesia is a fundamental human

right[50-54] (iv) the NHS commitment to deliver the right care to the right patient at the right time (v) the drive to reduce variation in the NHS (vi) the need to optimise emergency care pathways and deliver better care (vii) support from patient and public groups and charities.

Sustained interest and intent: Demand on Ambulance Services is increasing annually. Most patients accessing ambulance services report pain.[1] Ambulance paramedics report that their formulary is frequently inadequate.

New knowledge: Most trials of ketamine for analgesia are small, of insufficient quality and derive from North America or Australia. Patient expectation and approaches to health service delivery in these countries differ from the UK. No studies addressing cost-effectiveness have been published. We need to generate new knowledge specific to the NHS.

Generalisability and prospects for change: Our work will determine if ketamine is clinically effective in the hands of UK paramedics. It will inform policy makers, guideline developers and ambulance services if ketamine should be added to the paramedic formulary.

Building on existing work: This study builds on our experience delivering prehospital randomised controlled trials (RCTs). The PARAMEDIC trial,[60] a RCT of mechanical versus manual cardiopulmonary resuscitation, PARAMEDIC 2,[61] a RCT of adrenaline versus placebo in cardiac arrest and REPHILL a RCT of prehospital blood products currently underway.[62]

1.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to ICH Good Clinical Practice (GCP) guidelines. It will also comply with the Medicines for Human Use (Clinical Trials) Act 2004, subsequent amendments and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 2018.

The main ethical issues relating to this trial are the enrolment of patients who lack capacity to provide written, informed consent yet require urgent treatment. This situation falls under the provisions of the Clinical Trials Regulations (2006, No 2984) which allows for urgent actions to be taken for the purposes of the research when it is not reasonably practicable to obtain written informed consent. We will apply to a Research Ethics Committee flagged for considering research involving adults lacking capacity. We will work with them and our patient and public partners to develop an approach which protects the rights, safety, dignity and well-being of research participants and facilitates and promote ethical research that is of potential benefit to participants, science and society. We will use the framework which we co-developed with the Health Research Authority to summarise the key ethical issues.[73]

Capacity will be monitored and once the participant regains capacity written informed consent will be requested. If the participant does not regain capacity then written informed consent will be requested from a legal representative.

It is our assessment that the Medicines and Healthcare products Regulatory Agency (MHRA) trial category is a type A trial, which has no higher risk than that of standard medical care. Morphine is licenced for use in this patient population and ketamine is routinely used. The main additional burden of the trial protocol relates to the follow-up and completion of questionnaires about resource use and health related quality of life.

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, **357**: 1191-1194).

1.7 Assessment and management of risk

We believe the risks associated with this trial are of Type A, that is the risks are no higher than the risk of standard medical care. Morphine sulphate has been routinely used by paramedics for many years. Ketamine is increasingly being used by paramedics, however it is not yet a part of routine practice. To support this assertion we have included a copy of the national guideline for morphine sulphate and copies of local guidelines for ketamine hydrochloride at both participating ambulance trusts.

WCTU will complete a full risk assessment and develop a monitoring plan commensurate with the risks identified.

The treatment protocol has been developed to align with the current national clinical practice guidelines for pain management in adults produced by the Joint Royal College Ambulance Liaison Committee (JRCALC).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

This is a multi-centre, randomised, double blinded trial comparing the clinical and cost-effectiveness of ketamine and morphine for severe pain in acute traumatic injury. It is a pragmatic, phase III trial working with two large NHS ambulance trusts with an internal pilot. Participants will be followed up for 6 months.

Adult patients ($\geq$16 years old) will be eligible for recruitment if they have severe pain due to acute injury, determined by a paramedic to require IV morphine or equivalent.

Patients will be randomised to either morphine or ketamine. Randomisation will occur when the trial IMP pack has been opened.

All survivors who consent to continue participation in the trial will be contacted to take part in the follow up at 3 and 6 months.

Figure 2 Trial flow diagram

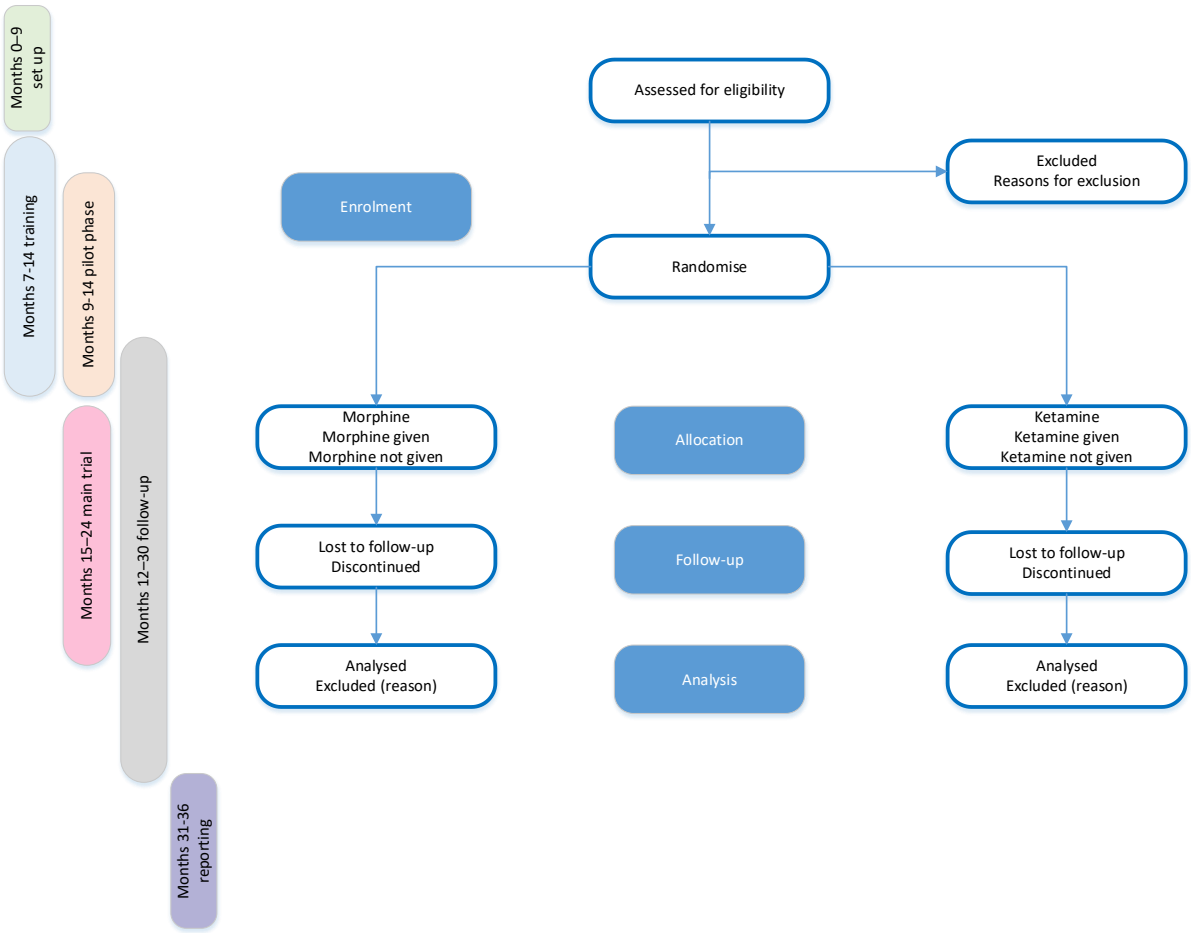


Figure 3 Treatment at time of incident/ injury

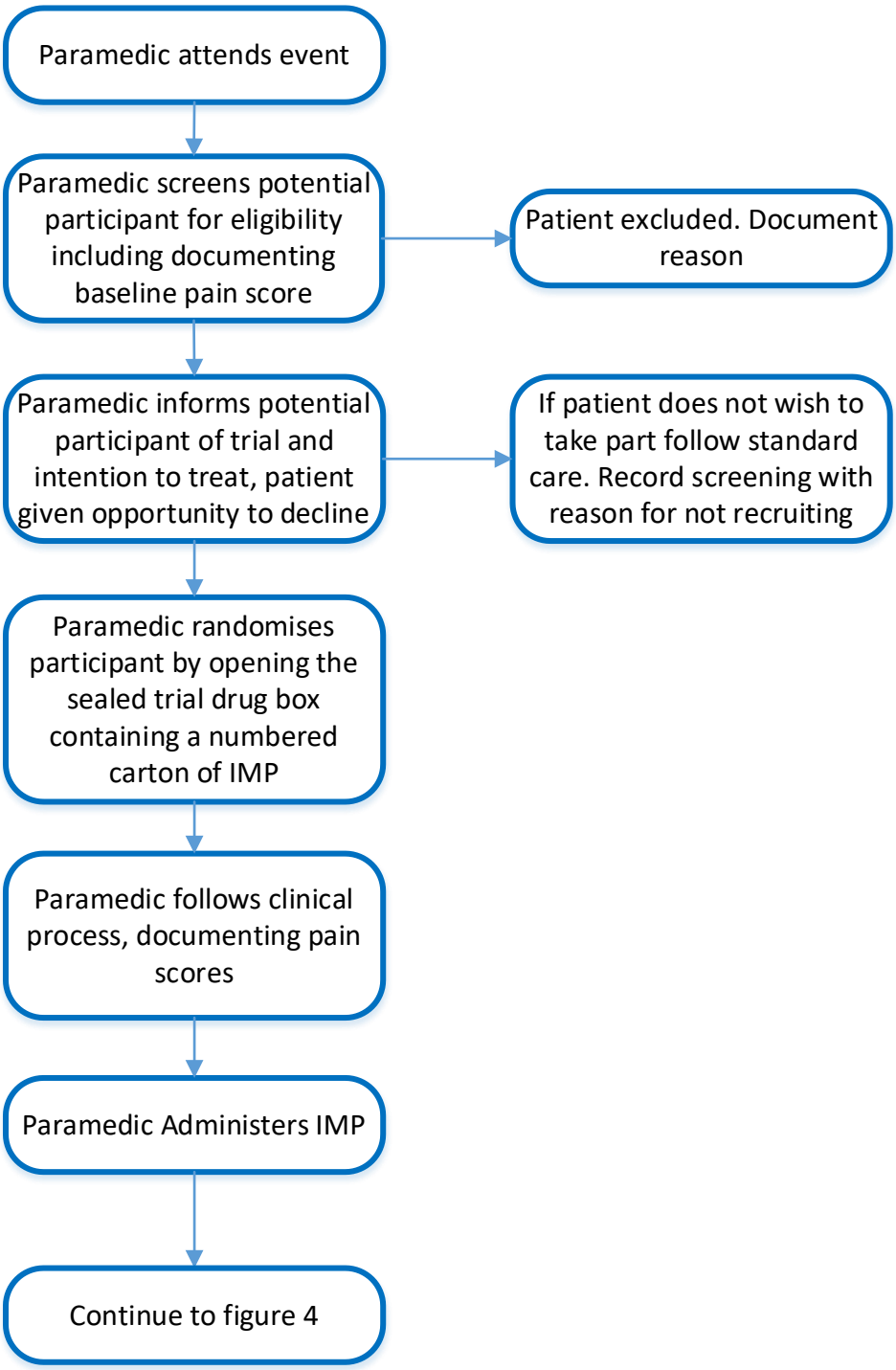
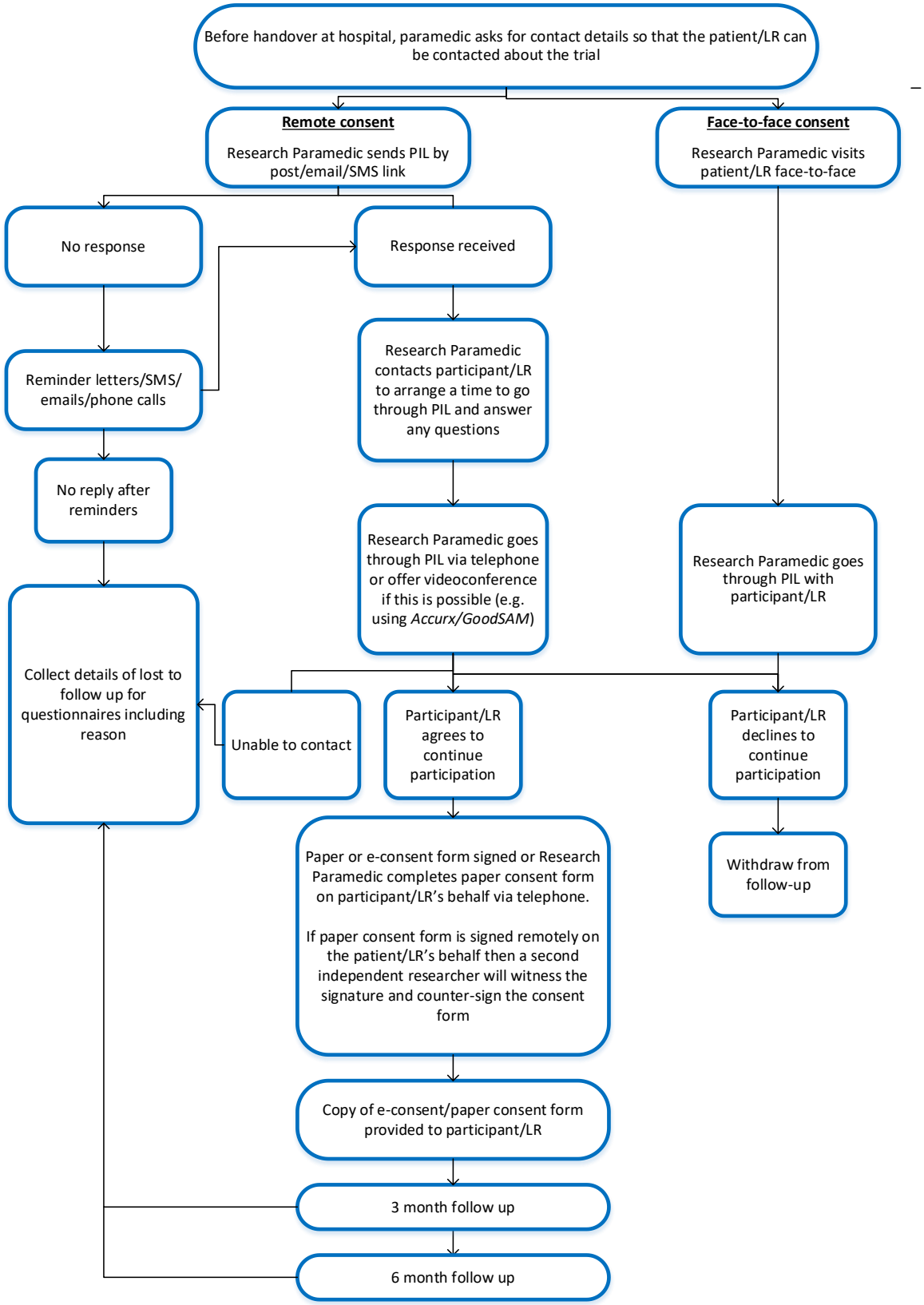


Figure 4 Consent post treatment and Follow up (continued from figure 3)



2.2 Pilot study

The main PACKMaN trial will be preceded by an internal pilot to test the trial processes, including consent, randomisation, treatment and follow up. The pilot phase will run for 6 months from the first randomised patient.

We anticipate that by six months we will recruit a minimum of 84 patients (42 per patient arm). The pilot will take place at two ambulance hubs, one from each participating ambulance service. Recruitment rate is anticipated to be 4 patients per month, for every 50 paramedics trained in the trial. Success criteria for recruitment will be based on the traffic light system:

	Red	Amber	Green
Trial recruitment (% threshold)	<50%	≥50%	=100%
Number of sites opened	0	1	2

The following process measures for the pilot study will be reviewed by the Trial Steering Committee when considering the recommendation to funder for progression to the main trial:

- Data completeness for the primary and secondary outcomes
- Consent rate to continue in the long term follow-up
- Review of protocol non-compliances, adverse events and serious adverse events /reactions
- Tracking of IMP

On reaching the pre-defined recruitment success criteria and a satisfactory review of process measures, the TSC will recommend to the funder that the internal pilot runs seamlessly into the main trial. The pilot study results will be reported in the HTA Monograph in accordance with the CONSORT guideline for pilot studies. Patients recruited to the pilot study will be included in the analysis of the main study.

2.3 Aims and objectives

2.3.1 Primary objective

The primary objective of this trial is to determine whether paramedic administered ketamine or morphine provides more effective pain relief for patients reporting severe pain following trauma as measured by the Sum of Pain Intensity Difference (SPID), assessed using a 0-10 numeric rating scale. The numerical rating scale is used to record the severity of pain in NHS Ambulance services. Sum of Pain Intensity Difference and the 0-10 numerical rating scale are advocated by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.[63] Pain intensity will be recorded prior to treatment administration and then at regular intervals following randomisation until arrival at hospital.

2.3.2 Secondary objective

Secondary objectives of the trial are to assess the effects of paramedic administered ketamine or morphine on overall pain relief / patient experience, tolerability, resource used, longer term outcomes and cost effectiveness.

Secondary objectives are to assess the effects of paramedic administered ketamine and morphine on clinical, patient-centred outcomes as advocated by IMMPACT[63] and European Medicines Agency[64] and economic outcomes up to 6 months post randomisation. These will address all the outcomes identified in the HTA commissioning brief and provide a definitive assessment of the clinical and cost effectiveness of these two treatment options.

2.4 Outcome measures

Primary Outcome

Effectiveness of pain relief from randomisation to arrival at hospital as measured by Sum of Pain Intensity Difference (SPID) score (using a 0-10 numerical rating scale)

Secondary Outcomes

Effectiveness of pain relief and overall patient experience from randomisation to arrival at hospital

- Total Pain Relief (TOTPAR) score
- Time to perceptible analgesia
- Time to meaningful analgesia
- Time to peak analgesia
- Duration of analgesia
- Requirement for rescue analgesia
- Proportion of patients with a pain intensity score below 4/10 (0-10 numerical rating scale (NRS)) on arrival at hospital
- Vital signs (oxygen saturation, blood pressure, heart rate, respiration rate, Glasgow Coma Scale)
- Patient Global Impression of Change on arrival at hospital

Incidence of side effects and adverse events

- Airway: vomiting, aspiration, advanced airway management
- Respiratory: desaturation, need for ventilatory support
- Cardiovascular: arrhythmia, hypotension and hypertension
- Neurologic: sedation, excitatory movements, adverse behavioural reactions
- Other: nausea, allergic reaction

Resource use

- Ambulance job cycle time (scene arrival to arrival at hospital)
- Number of ambulance resources (technicians, paramedics, doctors and vehicles) in attendance
- Cumulative IMP doses administered
- CT scan use
- Hospital or ICU admission
- Length of stay ED, ICU, Hospital

Longer term outcomes

- Chronic pain using BPI-SF at 3 & 6 months from randomisation
- Health-related quality of life EQ-5D-5L and CSRI at 3 and 6 months from randomisation
- Cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained using EQ-5D 5L and CSRI (at 3 and 6 months post randomisation)

2.5 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.5.1 Inclusion criteria

1. Age ≥16
2. Patient reports a pain score ≥7/10 on a 0-10 NRS following acute traumatic injury
3. Intravenous (IV) or intraosseous (IO) access obtained
4. Determined by a paramedic to require IV morphine or equivalent

2.5.2 Exclusion criteria

1. Known or suspected pregnancy
2. Unable to articulate severity of pain using the 0-10 NRS
3. Lack of capacity due to a reason other than pain
4. IV/IO ketamine or opioid analgesia immediately prior to randomisation*
5. Known contraindication to either ketamine or morphine as per the SmPC**
6. Patient declines participation
7. Known prisoner

* This criterion is intended to exclude only those patients administered ketamine or opioids via IV/IO route immediately prior to randomisation.

**SmPC is the abbreviation for Summary of Product Characteristics

2.6 Participant identification / Screening

Patients will be screened based on the inclusion/exclusion criteria and if eligible randomised to the trial. Identification, screening and randomisation will be undertaken by the paramedics who are the usual care team.

On completion of a clinical case the paramedic will advise the research team, via a locally agreed process, that a patient has been recruited to the trial.

2.7 Site Staff Training

Potential participants will be identified by the attending paramedic and if eligible will be enrolled into the trial. The participant, when capacity is regained, or a legal representative will be consented later by the research paramedic.

Training will be provided to the paramedics and research paramedics and will help standardise recruitment processes, trial treatments and patient care, and ensure accurate, complete and reliable data are collected.

Training will be provided for the paramedics to assist with screening the patient for inclusion into the trial. This will include information on the contraindications to ketamine and morphine according to the Summary of Medical Product Characteristics (SmPC). Guidance will also be provided for situations where ketamine / morphine should be used with caution and where adjustment to dosage may be required.

Training will include online learning materials, which will remain accessible to participating paramedics throughout the trial. Delivery of training to participating paramedics at collaborating sites will be the responsibility of each participating Ambulance Trust and the research paramedic. Quality assurance procedures and process evaluation will be put in place to ensure training is delivered in a standardised manner.

Educational and trial related training material will be developed to support research staff at the site initiation visit. In addition to this Warwick CTU will provide advice and support to the local Principal Investigators (PI) and research staff with training on the protocol, completion of the CRF and trial procedures including standard operating procedures (SOPs); provide instructional material to trial site; and instruction on the protocol and training manual. Training materials including slide shows, videos, FAQs and written material will be available. Training will be recorded online through the trial website and act as the training log. New staff joining the trial will be trained by the research paramedic at the site and will be given access to an online learning materials for the rest of the duration of the trial.

2.8 Informed consent

Acute severe pain disrupts cognitive function, reducing the ability to self-regulate one's thoughts, feelings, and behaviours leading to impaired mental capacity.[66,67] [68]Many patients will also be physically incapacitated and unable to provide written informed consent due to the nature of their injuries (e.g. broken arm) or location (e.g. trapped in the wreckage of a car). Patients with severe pain require urgent treatment to relieve pain for humanitarian reasons as well as to reduce the physiological stress caused by severe pain. The urgency with which treatment for acute severe pain must be provided precludes it being practical to obtain written informed consent from either the patient or a personal legal representative as to do so would delay treating the patient's pain. In addition, the enrolling paramedic will not have timely access to a professional legal representative making such an approach impractical.

It is our assessment that it is necessary to take action for the purposes of the clinical trial as a matter of urgency, and it is not reasonably practicable to meet paragraphs 1 to 5 of Part 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004(c). As a consequence we believe this trial is consistent with the requirements for Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006.

Consent process: (figure 3 and 4)

Pre-randomisation

Before recruiting any patient to the trial, the paramedic will provide the patient with brief verbal information about the trial by reading predefined text from an aide memoire (Brief PIL for Paramedics), and advise the patient of their intention to enrol the patient into the trial. At this time, the paramedic will not be seeking informed written consent but will provide the patient the opportunity to decline participation in the trial. The paramedic will document the patient decision to decline participation or participate in the trial in the patient report form/clinical notes. If the patient declines further participation in the trial, then no further trial investigations will be administered and standard care will be provided without prejudice.

If the patient does not decline participation, the paramedic will proceed to open the trial drug pack and randomise the patient into the trial. Clinical care will be provided in line with usual care while the trial IMP will be administered according to the trial protocol. The serial number of the trial IMP will be documented in the patient report form/clinical notes. Before the patient is handed over at the receiving hospital the enrolling paramedic will collect their contact details in order for the Research Paramedic to make further contact about the trial and provide a copy of the PIL. On handover to the hospital, hospital staff will be notified that the patient has received trial related IMP.

Face-to-face consent

If the patient has been admitted as an inpatient, or if the patient requests a home visit, the research paramedic can visit the patient face-to-face and provide the patient with a participant information sheet, allow the patient time to consider their options and answer any questions the patient may have. If the patient declines consent then they will be withdrawn from further follow-up and no further contact will be made. If the patient would like to continue their participation in the trial then written informed consent will be requested. If the patient's injuries prevent written informed consent (e.g. due to injury to the dominant hand) then informed verbal consent will be witnessed and the consent form will be counter-signed by the witness. A copy of the consent form will be provided to the patient, a copy will be kept in the hospital medical notes and a copy will be filed in the Trial Site File.

If the Research Paramedic determines that the patient lacks capacity to provide informed written consent then they will seek consent from a personal legal representative. The Research Paramedic will provide the personal legal representative with verbal and written information to enable them to make an informed decision on behalf of the patient. If no personal legal representative is available or willing to consent on behalf of the patient, then the Research Paramedic will obtain consent from an approved professional legal representative un-connected to the trial.

Remote consent

Alternatively, If the patient was not admitted to hospital, has already been discharged from hospital or it is not practicable to contact them face to face, then the research paramedic will send the Patient Information Sheet via post to the patient's home address or electronically e.g. via email, or SMS link. If a letter is sent this will include a reply slip and details for the patient to call, so that the patient can indicate whether they are happy to be contacted about the trial. If they choose not to be contacted then no further contact will be made. Three attempts can be made to contact the person via telephone, email or SMS. If no reply is received then a single reminder letter will be sent/made to the patient. If there is no response then no further contact will be made.

Once the research paramedic has made contact with the patient they will go through the Patient Information Sheet, allow the patient time to consider the trial and answer any questions the patient may have. This discussion will be done over the telephone, or by videoconference if possible using a telemedicine platform such as *Accurx* or *GoodSAM*. Once the patient has decided they have had sufficient time to consider their options they will be asked whether they wish to continue their participation in the trial or not. If the patient declines consent then they will be withdrawn from further follow-up and no further contact will be made.

If the patient would like to continue their participation in the trial then written informed consent will be requested remotely. If the patient has access to a computer, smart phone or tablet they will be sent a link to an e-consent form (designed on Qualtrics) to sign. The Research Paramedic will then add their e-signature on the consent form and provide a copy to the patient. If the patient is unable to sign an e-consent form then the Research Paramedic will complete the consent form on the patient's behalf and this will be observed by a 2nd independent witness who will also counter-sign the consent form. A copy of the completed consent form will be given to the patient and a copy will be retained for the Trial Site File.

If the Research Paramedic determines that the patient lacks capacity to provide informed written consent then they will seek consent from a personal legal representative. The paramedic will provide the personal legal representative with verbal and written information to enable them to make an informed decision on behalf of the patient. If no personal legal representative is available or willing to consent on behalf of the patient, then the paramedic will obtain consent from an approved professional legal representative un-connected to the trial.

2.9 Randomisation

2.9.1 Randomisation

Randomisation will be provided by the Programming Team at the Warwick CTU. Randomisation will be achieved by way of specially prepared, sequentially numbered treatment packs containing identical ampoules of either morphine (comparator) or ketamine (intervention). The content of the drug packs will be determined from a randomisation list prepared by the programming team at the trials unit. The randomisation sequence will be stratified by ambulance service to ensure a ratio of 1:1 control:intervention. Distribution of trial drug packs by the trial drug manufacturer will ensure equal proportions of morphine (comparator) and ketamine (intervention) are distributed to each participating site. Allocation will be concealed from study personnel, ambulance staff and patients.

Numbered study drug packs in a pre-randomised sequence, will be carried by participating ambulance paramedics. Randomisation will be achieved by opening the pack. This avoids the need for any randomisation procedures before recruitment which could delay patient treatment.

2.9.2 Post-randomisation withdrawals, exclusions and moves out of region

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Participants may be withdrawn from the trial treatment at the discretion of the investigator and/or Trial Steering Committee due to safety concerns.

If at any point following enrolment the patient (or their legal representative) indicates that they no longer wish to participate usual care will be provided. This will be logged on the database from the point they withdraw and no further contact will be made. All non-identifiable data up to the point of withdrawal will be retained in accordance with the trials regulations and included in the analysis unless otherwise indicated. No further data collection will be conducted from this point onwards. The information sheet explains the trial and the data that will be collected.

2.10 Trial treatments / intervention

2.10.1 Trial treatment(s) / intervention

Ketamine hydrochloride will be supplied in glass ampoules containing 15mg in 1ml and supplied in numbered treatment packs containing 3 ampoules (up to 2 for administration and 1 in case of breakage). The manufacture, clinical trials packaging, labelling and Qualified Person (QP) release will be arranged by MODEPHARMA. The ampoules will be labelled as trial related IMP and as such will be identical in appearance to morphine. Further details about the IMP can be found in the IMP dossier. Ambulance guidelines indicate that the analgesic dose of Ketamine is 0.2-0.5 mg / kg. The IMP can be administered by the intravenous (IV) or intraosseous (IO) routes.

Dosing regime

Paramedics will dilute the ampoule of ketamine hydrochloride with 9ml of 0.9% sodium chloride in a 10ml syringe. (Syringe 1).

Syringe 1 will be administered by slow IV / IO injection over 4 to 5 minutes. Titrate to effect (up to the full 10ml being administered) aiming to give the minimal effective dose.

Observe patient for at least 5 minutes for effect. If pain is not relieved after syringe 1 has been administered, prepare a second syringe by diluting a further ampoule of ketamine hydrochloride with 9ml of 0.9% sodium chloride in a 10ml syringe. (Syringe 2).

Administer 2 ml aliquots from Syringe 2 by slow IV / IO injection every 5 minutes. Repeat further 2ml aliquots every 5 minutes until adequate pain relief is achieved.

If after adequate pain relief is achieved the person experiences breakthrough pain, further 2ml aliquots may be administered every 5 minutes.

The maximum dose that can be administered under this protocol is 30mg (two ampoules).

A reduced dose, titrated to effect, should be administered if actual or estimated weight is less than 50kg or any of the conditions where caution is advised in the use of ketamine or morphine are present.

Ketamine 15mg/ ml				
Indicative times (min)	Volume (ml)	Dose (mg)	Cumulative dose (mg)	Dose in 75kg person (mg/kg)
0-5	10	15	15	0.20
10 to 15	2	3	18	0.24
15 to 20	2	3	21	0.28
20 to 25	2	3	24	0.32
25 to 30	2	3	27	0.36
30 to 35	2	3	30	0.40

(Figure 5) Ketamine dosing table

Rationale for proposed doses and infusion times: The dose rationale is selected to align with JRCALC guidelines. These guidelines advise that ketamine should be administered over at least 30-60 seconds as rapid administration may cause respiratory depression, apnoea or enhanced pressor response. The PACKMAN protocol allows analgesia to be administered more slowly (over 4-5 minutes for the initial dose) which should avoid these complications.

The initial recommended dose for Ketamine is 0.2mg/kg which can be repeated (if necessary up to 0.5mg/kg for analgesia). The dosing regime described for PACKMaN provides a dose of 0.2-0.4mg/kg for a 75kg person and 0.15-0.3 mg/kg for a 100kg person. Titrating analgesia to effect and using with caution in participants who are < 60kg should reduce the risk of causing sedation (the main consequence when the dose of ketamine exceeds 0.5 mg/kg).

2.10.2 Control intervention

Morphine sulphate will be supplied in glass ampoules containing 10mg in 1ml and supplied in numbered treatment packs containing 3 ampoules (up to 2 for administration and 1 in case of breakage). The manufacture and clinical trials packaging, labelling and QP release will be arranged by MODEPHARMA. The ampoules will be labelled as trial related IMP and as such will be identical in appearance to ketamine. Further details about the IMP can be found in the IMP dossier. Ambulance guidelines recommend administration by slow injection (rate of approximately 2mg per minute). The IMP can be administered by the intravenous or intraosseous routes.

Dosing regime

Paramedics will dilute the ampoule of morphine sulphate with 9ml of 0.9% sodium chloride in a 10ml syringe. (Syringe 1).

Syringe 1 will be administered by slow IV / IO injection over 4 to 5 minutes. Titrate to effect (up to the full 10ml being administered) aiming to give the minimal effective dose.

Observe patient for at least 5 minutes for effect. If pain is not relieved after syringe 1 has been administered, prepare a second syringe by diluting a further ampoule of morphine sulphate with 9ml of 0.9% sodium chloride in a 10ml syringe. (Syringe 2).

Administer 2 ml aliquots from syringe 2 by slow IV / IO injection every 5 minutes. Repeat further 2ml aliquots every 5 minutes until adequate pain relief is achieved.

If after adequate pain relief is achieved the person experiences breakthrough pain, further 2ml aliquots may be administered every 5 minutes.

The maximum dose that can be administered under this protocol is 20mg (two ampoules).

A reduced dose, titrated to effect, should be administered if actual or estimated weight is less than 50kg or any of the conditions where caution is advised in the use of ketamine or morphine are present (see section 2.7).

Morphine 10mg /ml				
Indicative times (min)	Volume (ml)	Dose (mg)	Cumulative dose (mg)	Dose in 75kg person (mg/kg)
0-5	10	10	10	0.13
10 to 15	2	2	12	0.16
15 to 20	2	2	14	0.19
20 to 25	2	2	16	0.21
25 to 30	2	2	18	0.24
30 to 35	2	2	20	0.27

(Figure 6) Morphine dosing table

Rationale for proposed doses and infusion times:

The dose rationale is selected to align with JRCALC guidelines. These guidelines advise that morphine should be administered by slow injection (rate of approximately 2mg per minute) up to 10mg for adults. Observe the patient for at least 5 minutes after completing of the initial (10mg) dose before repeating the dose if required.

2.10.3 Non-investigational medicinal product

Both morphine sulphate and ketamine hydrochloride have predictable side effects that may require subsequent treatment. Morphine sulphate may cause respiratory depression while ketamine hydrochloride may be associated with hallucinations as the drug wears off. Typically, opioid induced respiratory depression is treated with naloxone hydrochloride, while hallucinations secondary to ketamine administration are typically treated with midazolam hydrochloride. Both naloxone hydrochloride and midazolam hydrochloride will be available to paramedics as open-label medicines supplied by the ambulance service. The decision to administer either naloxone hydrochloride or midazolam hydrochloride will be a clinical decision by the paramedic.

Naloxone Hydrochloride
Presentation: two glass ampoules each containing 400mcg in 1ml
Initial dose: 400mcg (1ml)
Repeat dose: 400mcg (1ml)
Maximum cumulative dose: 4000 mcg
Midazolam Hydrochloride:
Presentation: one glass ampoule containing 5mg in 5ml
Initial dose: 1mg (1 ml)
Repeat dose: 1mg (1ml)
Maximum cumulative dose: 5mg (5ml)

2.10.4 Rescue and adjunctive analgesia

If required, rescue and adjunct analgesia will be provided from standard ambulance medications, supplied by the ambulance service, in accordance with JRCALC guidelines. In the first instance inhaled **entonox** will be provided. Entonox may be supplemented with up to 1g intravenous

paracetamol provided none has been administered within the previous 4 hours. The definitions for rescue analgesia and adjunct analgesia have been defined in the statistical analysis plan, prior to database lock and analysis. Rescue analgesia will be defined by the administration of open label ketamine or morphine before hospital arrival. Adjunctive analgesia will be defined as post-randomisation administration of entonox, paracetamol, ibuprofen prior to hospital arrival.

In all cases where rescue analgesia is required, we will monitor the response to rescue analgesia as per trial IMP.

2.10.5 Drug storage and dispensing

IMP packs will be stored within controlled drugs safes on ambulance stations. Each shift the paramedic will sign out a drug pack as per local policy for controlled drugs. All storage and recording regulations for controlled drugs must be complied with.

If a patient is recruited to the trial and unused trial IMP ampoules remain, the unused IMP will be destroyed as per local ambulance service policy and the destruction documented in the controlled drugs register.

2.10.6 Drug accountability

All uses of trial IMP packs will be documented on accountability logs. The trial will utilise ambulance service systems for documenting receipt, dispensing, returns and destruction of IMP packs.

The attending clinician will be required to document on the patient record the IMP pack number and how many ampoules were used from the IMP pack.

Trial IMP will be reconciled on station in the controlled drugs register and also with the trial database which detail patients who have been enrolled and the trial IMP packs that were used.

2.11 Blinding

2.11.1 Methods for ensuring blinding

The packaging and the labelling of the IMP packs will not give away which IMP is being used therefore the patient, attending clinicians, research paramedics and trial administration team will be blinded. Only the statistician and the programming team will be able to link the IMP pack number to the allocation of ketamine or morphine.

2.11.2 Emergency Unblinding

An emergency unblinding system has been established to provide the pre-hospital clinicians and ED clinicians immediate access to the participant's treatment allocation if required.

This will be organised via the emergency control room (or equivalent) of the participating ambulance service. The paramedics and emergency departments will be provided with contact details of the control room (or equivalent) who will have access to the unblinded treatment allocation via a web application developed by the WCTU programming team. In the event of a total server failure, the staff at the control hub/trauma desk will be instructed to phone the Chief Investigators and Co-Investigators at WCTU on a specifically allocated phone number which has been provided to the ambulance services. This phone line will be covered 24/7 by Michael Smyth, Gavin Perkins and Joyce Yeung, who will have a paper copy of the unblinding information. The paper copy will be in the form of wallet-sized scratch cards. On receiving a valid request to unblind, the foil next to the relevant

pack number will be scratched off to reveal the treatment allocation. All unblinding cards will be retained and returned to the trial office at the end of the recruiting period for review to ensure only allocations with authorised requests have been revealed. Following a backup emergency unblinding, the person carrying out the unblinding will also need to complete an internal excel spreadsheet unblinding log to record details of the event, as soon as possible after the event, and inform the trial team once completed.

The Chief Investigators retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Otherwise treatment codes (IMP pack number) will only be broken by the statistician at the request of the Data Monitoring Committee (DMC).

2.11.3 Methods for unblinding the trial – after trial completion

Requests for unblinding of treatment allocation may be received (either from survivors, legal representatives or from the next of kin of trial participants that have deceased) during the trial or after completion of the trial, by the PACKMaN trial office or Ambulance Services. Following completion of trial results analysis, the PACKMaN trial office will complete an unblinding request form for these participants. Unblinding will then be requested and carried out with CI (or CI delegate) oversight and approval. The treatment allocation will then be provided to the Ambulance Service who will then provide to the enquirer (once appropriate checks have been performed).

2.12 End of trial

The trial will end when all participants have completed their 6-month follow-up and collection of secondary outcomes is complete.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee and MHRA will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Visit	**1**	**2**	**3**	**4**
Visit Window (No. Weeks ± No. Days)	**Baseline/Pre hospital/Hospital arrival**	**After hospital arrival**	**3m (± 2w)**	**6 m (± 1 m)**
Trial Information	✓	✓		
Informed consent		✓		
Randomisation	✓			
Vital signs	✓			
Inclusion/exclusion criteria	✓			
Intervention	✓			
Rescue analgesia	✓			
Quality of Life – EQ-5D-5L			✓	✓
Side effects & Adverse events	✓	✓	✓	✓
Questionnaire – BPI-SF			✓	✓
Questionnaire – CSRI			✓	✓
SPID	✓			
TOTPAR	✓			
Time to perceptible analgesia	✓			
Time to meaningful analgesia	✓			
Time to peak analgesia	✓			
Duration of analgesia	✓			
Patient Global Impression of Change	✓			
Resource use	✓	✓	✓	✓

3.2 Data collection

3.2.1 Patient enrolment

All traumatic injuries where a trial pack is opened will be reported to the WCTU promptly. Mechanisms for providing this information will be specific to each ambulance service after being discussed and agreed in advance with WCTU.

3.2.2 Hospital

Patients may be taken to any hospital in the trial regions. Although hospital clinicians will not have a role in delivering the trial interventions, they will be informed about the trial and will be provided with information for any clinicians or patients that need it. As such, hospital staff involvement in the PACKMaN trial is very minimal. The main involvement will be as follows:

1. To maintain an awareness of the trial in ED, an ED leaflet is available
2. Identify a local collaborator who will act as a study support and main contact for the research paramedics
3. Report any SAEs, verbally or by email, to the ambulance services as soon as they become aware (research paramedics are responsible for completing SAE forms and providing to WCTU)

Prior to recruitment, hospitals in the trial region have been contacted to determine whether they have capacity to participate in the study or will decline participation.

3.2.2.1 Participating hospitals

Hospitals that have agreed to take part will assign a local collaborator for the trial who will assist/facilitate the collection of the following data by the research paramedics:

- SAEs
- CT scan use
- Hospital or ICU admission
- Length of stay ED, ICU, hospital

3.2.2.2 Hospitals that have declined participation

If a patient is likely to be taken to a hospital that has declined participation, they will still be eligible for recruitment providing that all other eligibility criteria are met. Patient safety is of utmost importance and there will be no delay in delivery of patient to a hospital based on whether the hospital is taking part in the trial or not. It will be emphasised to the paramedics that patients are taken to hospital as per routine clinical practice and there will not be any conflict of interest in this decision.

For hospitals who have declined to take part in the trial the following data may not be possible to collect for trial participants:

- CT scan use
- Hospital or ICU admission
- Length of stay ED, ICU, hospital

All patients recruited into the PACKMaN trial will have a wristband which contains the trial name and contact details for emergency unblinding and SAE reporting. ED staff will also be made aware that the patient is enrolled into the trial as part of the handover process from the paramedics.

3.2.3 Follow up

Participants will be followed up approximately 3 and 6 months after their injury as per the table in section 3.1. Questionnaire data will be collected from patients who provide informed written consent. An appropriately trained member of the research team will complete the Brief Pain Inventory – Short Form, Client Service Receipt Inventory (CSRI) and EuroQuol EQ-5D-5L questionnaire with the patient either in person, over the telephone, or the participant can return completed questionnaires in the post to WCTU or by email to the research paramedics (e.g. if initially provided by email). Data for questionnaires completed in person or over the telephone may be entered directly onto the database by the research paramedics. For completed questionnaires posted or emailed to WCTU, these will be retained by the clinical trials unit in accordance with WCTU policies and procedures ensuring compliance with UK GDPR and DPA requirements.

If the participant consents to contact via telephone, text message or email, they will be telephoned or sent an electronic prompt to encourage them to complete the questionnaire. If the completed questionnaire has not been returned after 2 weeks, where possible, the research paramedics will send out an electronic reminder and/or resend a copy of the questionnaire. If there is still no response, a further 2 reminders (telephone, text message or email) (with a suggestion of a 2-week interval between each contact) may be sent out before the patient is deemed lost to follow-up. In the event that there is no response to the 3-month questionnaire, the 6-month questionnaire will still be sent unless confirmed that the patient has withdrawn and/or has requested no further contact.

To ensure accurate, complete and reliable data are collected, the WCTU will provide training to site staff in the format of investigator meetings and site initiation visits. Quality assurance procedures and process evaluation will be put in place to ensure training is delivered in a standardised manner. The WCTU will provide the local PIs and research staff with training on the protocol, completion of the CRF and trial procedures including SOPs.

Participants will receive a voucher with their 3- and 6-month questionnaires. Vouchers will be provided regardless of whether or not questionnaires are completed or returned.

In addition to the follow up questionnaires, outcome data will be collected from the hospital of the ED where the patient was treated. Hospital data collection will be carried out by the research paramedics at hospital sites that have agreed to take part in the PACKMaN trial and/or have agreed to issue Letters of Access to the research paramedics. Local collaborators, assigned by the hospitals which have agreed to take part, will provide study support to the research paramedics for collecting this outcome data. For hospitals that have declined participation and have not agreed to issue Letters of Access, it will not be possible to retrieve the hospital data and this ‘planned missing data’ will be accounted for in the statistical analysis (see section 6).

4. PHARMACOVIGILANCE

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment/intervention.

4.1.2 Adverse Reaction (AR)

An Adverse Reaction (AR) is: 'All untoward and unintended responses to an investigational medicinal product related to any dose administered'.

4.1.3 Serious Adverse Events (SAEs), including Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARS)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Immediate intervention was required to prevent one of the above or is otherwise an important medical condition.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are considered to be related to the administration of the trial drug and are also unexpected i.e. their nature or severity is not consistent with the Reference Safety Information (RSI). There need only be an index of suspicion that the event is a previously unreported reaction to the IMP, or a previously reported but exaggerated or unexpectedly frequent adverse drug reaction.

4.2 Assessing and Reporting SAEs, SARs and SUSARs

Serious adverse events which are not related to the acute traumatic injury, or are complications resulting from the **IMP administration to 30 days post IMP** must reported to the PACKMaN Trial team as soon as possible and **within 24 hours** of the research staff becoming aware of the event.

For each **SAE, SAR or SUSARs** the following information will be collected from the investigator site:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator

Any change of condition or other follow-up information should be sent to the PACKMaN Trial team as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

SAEs, SARs and SUSARs will be reported using the SAE form in the participant's CRF. The Principal Investigator or an appropriate delegate in each centre must report any SAEs, SARs and SUSARs to the trial coordinating centre within 24 hours of them becoming aware of the event. The SAE form should be completed and sent to WCTUQA@warwick.ac.uk. The trial manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting SUSARs to the sponsor, REC and MHRA within required timelines.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

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

Responsibilities are as follows:

- **Principal investigator or clinically qualified delegate**: assess causal relationship to administration of IMP based on knowledge of drug and patient.
- **CI or clinically qualified delegate**: also assess causality based on knowledge of drug and protocol. The CI or delegate cannot change the assessment by the PI or their delegate.
- **Appropriately trained WCTU team members**: will assess expectedness against the Reference Safety Information if it is deemed there is at least a possibility of causal relationship.

4.2.1 SAEs Exempt from Reporting

The trial is enrolling patients with acute traumatic injuries which may be immediately life threatening, or result in hospitalisation, persistent or significant disability / incapacity and or death. The IMP is used at one time point only, there is no ongoing treatment and both drugs are routinely used for pain management.

The following adverse events are captured on the case report form as secondary outcomes. If deemed serious they will also be recorded and reported using the SAE form.

- Airway: vomiting, aspiration, advanced airway management
- Respiratory: desaturation, need for ventilatory support

- Cardiovascular: arrhythmia, hypotension and hypertension
- Neurologic: sedation, excitatory movements, adverse behavioural reactions
- Other: nausea, allergic reaction

All serious adverse events should be reported with the exception of those which are expected to occur in this population as a direct result or consequence of their traumatic injury. Examples include (but are not limited to) admission to hospital for treatment of traumatic injury, complications of the traumatic injury (e.g. compartment syndrome, wound infection, acute respiratory distress syndrome, ventilator associated pneumonia).

4.2.2 4.2.2 Reference Safety Information

Section 4.8 of the approved SmPC for each IMP will be used to assess the expectedness of events. Updates to the SmPC will be reviewed, an assessment of the risk will be carried out and a decision whether to update the RSI will be made and documented. Any subsequent changes to the RSI will be subject to a substantial amendment prior to implementation.

4.3 Responsibilities

Principal Investigator (PI):

Checking for SAEs and SARs.

1. Using clinical judgement in assigning seriousness and causality
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using clinical judgement in assigning an independent causality assessment
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Common Terminology Criteria for Adverse Events (CTCAE) or Body System coding to all SAEs and SARs if not done by the PI as part of the data collection activities.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor or delegate:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Expectedness assessment of SARs
3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

5. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
6. Notifying Investigators of SUSARs that occur within the trial.
7. Checking for updates to the Reference Safety Information for the trial in line with the Trial Monitoring Plan.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.4 Procedures in case of overdose

Overdoses come under 'Patient Safety Incidents' and are defined as 'any unintended or unexpected incident which could have or did lead to harm for one or more patients' (also may be referred to as adverse incidents, clinical errors or near-miss). Although not a requirement of the CT regulations, the PI at each centre should ensure their NHS Trust is notified of any patient safety incidents, according to local policy and should inform WCTU within 24 hours of becoming aware of the incident.

4.5 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive - method. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the trial.

All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE.

Although pregnancy is not a contra-indication for either ketamine hydrochloride or morphine sulphate in the BNF, as this is a clinical trial, patients who are known or suspected to be pregnant will not be eligible to participate in the trial and will receive usual care. However, we recognise that a potentially eligible patient may not suspect that they are pregnant. In this scenario the paramedic would most likely not be able to identify a reason for exclusion, and the patient would be enrolled the trial. If, after enrolment in the trial the patient discovers that they are pregnant, and the trial team is made aware, we will inform the patient's general practitioner and antenatal team that the patient received a trial drug, provided the patient consents to us doing so.

4.6 Notification of deaths

Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate upon Warwick CTU being notified by the site.

4.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

A substantial amendment will be submitted within two weeks of the notification to the MHRA and relevant REC.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with GDPR, the 2018 Data Protection Act and WCTU SOPs.

5.1 Data collection and management

Bespoke CRFs will be designed by the Trial Manager in conjunction with the CI, Statistician and local PIs to ensure consistent data are captured through the trial. This will capture baseline characteristics (demographics, pain scores, patient impression of change, randomisation number, amount of IMP given, side effects)

Follow up data collection will include EQ-5D-5L and BPI-SF questionnaires at 3 and 6 months post injury, side effects, CT scan use, hospital or ICU admission, length of stay in hospital.

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, ambulance service records and hospital records (from which secondary outcome data will be collected from). CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data).

On all trial-specific documents, other than the signed consent form, the participant will be referred to by the trial participant number/code, not by name. Data will be entered on to the trial database by the research team.

Patients will be contacted either by post, telephone, email or text message for missing questionnaires and the research team will work with the hospitals to collect secondary outcome data.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff. The database will be tested and validated in accordance with the WCTU SOPs for secure data management.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Any paper data forms will be stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data will be stored in a secure area of the server with access restricted to staff working on the trial and the WCTU Quality Assurance team. All

databases containing identifiable information will be encrypted and password protected. Any data that are transferred out of the secure environment will adhere to WCTU SOPs.

On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number, not by name.

5.4 Data access and quality assurance

Data on enrolled participants will be stored securely at WCTU in accordance with GCP, the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. Participants will be identified by code only.

5.5 Data Shared with Third Parties

The trial statisticians and DMEC will have access to the dataset for the analysis of trial outcomes. Once the main analyses have been undertaken, deidentified individual participant data will be available to principal and other investigators subject to approval of data analysis plans by the TSC and compliance with the University of Warwick SOPs on Data Management and Sharing. We will comply with Data Sharing Policies that may be instituted by the NIHR during the lifetime of the project.

The datasets generated and/or analysed during the current study will be available upon request from the WCTU Data Sharing Committee (email: WCTUDataAccess@warwick.ac.uk) 6 months after the publication of the funder report, upon application to the WCTU Data Sharing Committee. The data will be a cleaned and anonymised only dataset and will be available for unrestricted use.

5.6 Archiving

Trial documentation and data will be archived for at least ten years after publication of the trial.

Trial documentation and data will be archived for at least ten years by the coordinating centre and at sites after completion of the trial. Anonymised electronic data sets will be stored indefinitely.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

Sample size calculation:

The International Association for the Study of Pain have quantified clinically meaningful improvements in pain intensity.[69] Improvements in Pain Intensity Difference (PID) with respect to pain score (PID, 0 – 10 NRS) and with respect to percent change (%PID) are reproduced below in Table 1 and Table 2 respectively.[69]

Table 1 Improvement in pain intensity relative to baseline pain (PID, 0 – 10 NRS)

	Baseline pain intensity (95% CI)	
PID	Moderate pain (95% CI)	Severe pain (95% CI)
Minimal improvement	1.3 (1.2 -1.4)	1.8 (1.7 – 1.9)
Much improvement	2.4 (2.2 – 2.6)	4.0 (3.9 – 4.1)
Very much improvement	3.5 (3.3 – 3.8)	5.2 (5.0 – 5.4)

Table 2 Improvement in pain intensity relative to baseline pain (%PID)

	Baseline pain intensity (95% CI)	
%PID	Moderate pain (95% CI)	Severe pain (95% CI)
Minimal improvement	20.1% (18.1% - 22.2%)	20.3% (19.0% - 21.6%)
Much improvement	34.7% (32.7% - 36.8%)	44.4% (43.2% - 45.6%)
Very much improvement	45.0% (43.1% - 46.8%)	56.1% (53.9% - 58.4%)

Improvements in PID range from 1.3 to 5.2, whereas improvements in %PID range from 20.1% to 56.1%, depending upon baseline pain intensity and improvement in pain intensity experienced by the patient. In line with IMMPACT recommendations, our primary outcome reports Sum of Pain Intensity Difference (SPID), which can also be reported as maximum percent change in Sum of Pain Intensity Difference (%SPID). Existing data indicate that improvement in %SPID is equivalent to improvement in %PID.[70] Therefore, to ensure our study is able to detect at least a 20% improvement in %SPID, regardless of baseline pain intensity, our sample size calculation is powered to detect 20% improvement in %PID, which in turn is equivalent to a 1 point difference (0 – 10 NRS) in effectiveness between morphine and ketamine.

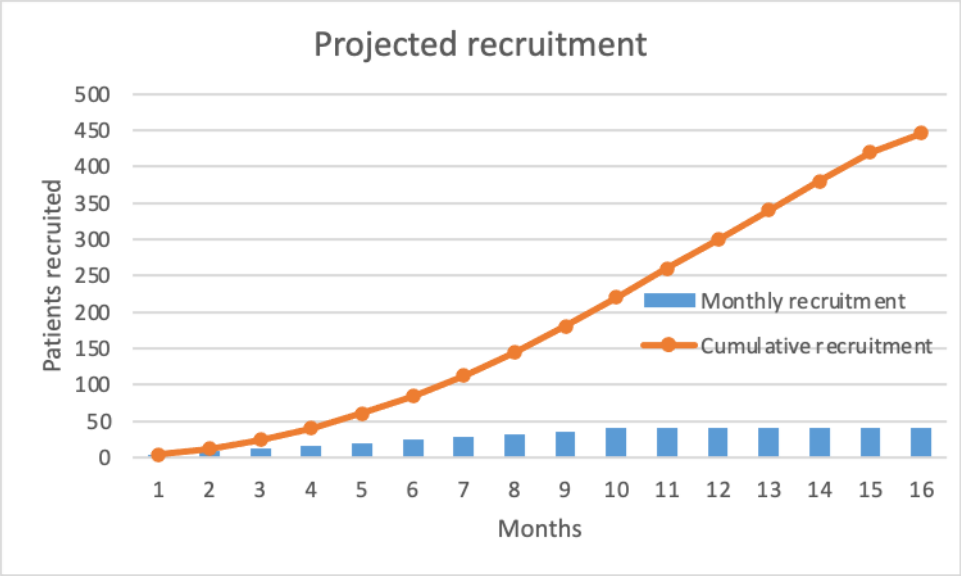
Previous randomised controlled trials comparing ketamine and morphine have adopted a standard deviation of 3.0 (Le Cornac, Motov and Sin). Our review of existing prehospital studies identified that the average non-response/withdrawal rate was 14%. We therefore calculate our sample size assuming a standard deviation of 3.0, 1:1 randomisation, a power of 90%, significance level of 5% and a withdrawal/non-response rate of 15%.

Based on these estimates we calculate our trial will require a sample of 446 subjects, recruiting 223 to each arm of the study, to detect a 1 point difference (0 – 10 NRS) in effectiveness between morphine and ketamine.

6.2 Statistical analysis of efficacy and harms

6.2.1 Planned recruitment rate

Our 12 month service evaluation of West Midlands Ambulance Service (WMAS) indicates that 7,611 patients received morphine to manage severe pain following trauma. Within WMAS, ambulances are deployed from 15 ambulance hubs. Larger hubs operate with 250 paramedic staff. Assuming even distribution across WMAS, each hub will manage 506 trauma patients with morphine, and each paramedic will therefore administer morphine approximately twice each year for severe pain following trauma. This equates to 0.16 administrations of morphine for trauma per month, per paramedic. In order to recruit 446 patients over 16 months, our trial seeks to recruit 48 patients during the 6 month pilot phase and a further 398 patients during the 10 months of the main trial. Our study proposes to recruit 500 paramedics (250 from each ambulance trusts) to participate in the trial. In order to recruit 446 patients over 16 months each participating paramedic will therefore need to recruit 0.056 patients per month. To accommodate a staggered implementation we have increased this recruitment target to 0.08 patients per month, per paramedic (half the rate identified in our service evaluation). Following discussion with our partner ambulance trusts, we expect each participating trust to train 25 paramedics to participate in the trial each month. Assuming a recruitment rate of 0.08 patients per month, per paramedic, this equates to 4 patients in the first month, increasing each month by a further 4 patients for every additional 50 paramedics trained. By 6 months (maximum duration of pilot phase) we expect 300 paramedics to be participating, and up to 84 patients to have been recruited. All 500 paramedics should be trained by month 10, when monthly recruitment will plateau at 40 patients per month (see figure 7).



(Figure 7) Projected recruitment

Recruitment and retention will be reviewed on a monthly basis in the Trial Management Group meeting and will be closely reviewed by the independent monitoring committees as well as the representatives from HTA. A CONSORT flow diagram will display the recruitment and retention in the study.

6.2.2 Statistical analysis plan

In brief, the SPID will be calculated for each patient as the area under the curve (from time of randomisation to the intervention to arrival at hospital). This outcome will be continuous and treatment difference will be assessed using linear regression models. Both unadjusted and adjusted

(for important covariates) estimates and 95% confidence intervals for the treatment effect will be obtained.

6.2.3 Secondary outcome analysis

Analysis of secondary outcomes which are continuous will be carried out in a similar way to the primary outcome. In the case of categorical outcomes, logistic regression models will be used to obtain treatment effects (unadjusted and adjusted). In the case of large skewed data, where the standard deviation is larger than the mean, we will use the negative binomial models. Time to event data will be presented as Kaplan Meier plots and analysed by Cox's proportional hazard method.

No formal interim analysis will be conducted. However, all outcomes will be reviewed by the Data Monitoring Committee through an open and closed report. The timing and frequency of the informal interim analyses will be discussed and agreed with the DMEC members and will include an introduction meeting at the start of the project and a meeting following the internal pilot.

Exploratory analysis will be reported using 99% confidence intervals. Logistic regression will be used with interaction terms (treatment group by sub-group) to assess the sub-group effect. The exploratory sub-groups assessed will be:

- Age (<60; ≥60 years)
- Injury severity (as demonstrated by patient data submitted to Trauma Audit and Research Network (TARN))
- Gender (male, female, Transgender, other, not disclosed)
- Alternative parenteral analgesia prior to randomisation (yes, no)

6.3 Interim analysis and criteria for the premature termination of the trial

No formal interim analyses are specified for this study.

6.4 Procedure(s) to account for missing or spurious data

A full statistical analysis plan will be initiated which will detail how sensitivity analyses that will be conducted to assess missing data and 'planned' missing data (i.e. hospital data from hospitals that have declined participation). This analysis plan will be finalised and approved by the Data Monitoring Committee. We will also aim to publish the statistical analysis plan in a reputable journal.

6.5 Health Economic Evaluation

Our economic evaluation will take the form of within-trial cost-effectiveness analyses, conducted from the perspective of the UK NHS and personal social services.[71] Estimates of economic costs will capture resource use associated with the pre-hospital emergency response and broader utilisation of hospital and community-based health and social care services. Resource use in the pre-hospital stage will be extracted from trial case report forms completed by research paramedics. This will include the number of paramedic staff, technicians, doctors and ambulance vehicles in attendance, duration of emergency response and cumulative morphine or ketamine doses administered. Resource use questions completed by participants at each assessment point during the study follow-up will provide a profile of all hospital inpatient and outpatient services, community health and social care encounters, prescribed medications, NHS supplies, time off work and out of pocket medical expenses. Health-related quality of life will be measured using the EQ-5D-5L at three and six months after randomisation. Patients meeting our inclusion criteria will not be able to complete

patient-reported questionnaires at the time of randomisation. Assessment of health-related quality of life at baseline will therefore be problematic. We will predict health-related quality of life at or immediately after randomisation from the baseline pain intensity score using published algorithms.[72] We will estimate QALY profiles for each participant over a six-month time horizon using the baseline-adjusted area-under-the curve method. We will fit a bivariate regression of costs and QALYs, with multiple imputation of missing data. We will estimate the incremental cost per QALY gained for the comparator interventions from incremental costs and incremental QALYs generated from the regressions. Cost-effectiveness estimates will also be generated for clinically meaningful subgroups including age, injury severity and gender.

Acute pain impacts functional recovery and contributes to post-injury disability. Long term patient outcomes including chronic pain, anxiety, depression and post traumatic distress disorder have been linked to inadequate early pain management.[5,6,55,56] With a time horizon of 6-months, our within-trial analysis may not fully capture the long-term impact of post-injury disability associated with inadequate acute pain management. If, during the time horizon of our study, robust evidence emerges from longitudinal studies indicating an adverse relationship between inadequate early pain management and longer-term effects, then we will develop a longer-term economic model. If so required, we will develop a cohort simulation model to simulate economic costs and consequences associated with post-injury disability over the life-time of patients. Model inputs will include intervention costs and health outcomes estimated from the trial, the probability of developing post-injury disability conditions (e.g. chronic pain and post-traumatic stress conditions) and associated costs and health related quality of life impacts. We will populate the model with data from the trial, supplemented by external evidence. Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis, and the probability of cost-effectiveness of ketamine will displayed through cost-effectiveness acceptability curves.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will act as the Sponsor for the trial. The trial will be managed according to the Warwick SOPs.

7.2 Regulatory authorities/ethical approval

Applications for approval of the trial will be made to the Medicines and Healthcare products Regulatory Agency (MHRA),, Research Ethics Committee (REC) and Health Research Authority (HRA).

All required ethical and regulatory approval(s) for the trial will be sought using the Integrated Research Application System.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS/Health and Social Care (HSC) Organisation's research management function (e.g. Research & Development (R&D) department). Warwick Clinical Trials Unit will only activate a site to recruitment once written confirmation of the NHS/HSC Organisation's agreement to participate in the study.

Any amendments will be reviewed and agreed by relevant parties before being submitted to the MHRA, REC and HRA as applicable. Approved amendments will be shared with the trial sites for acknowledgement and implementation.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. Annual DSURs will be submitted annually to the MHRA within 60 days of the anniversary date of MHRA approval. The authorities (REC/MHRA) will be notified of the end of the trial (whether at planned time or prematurely).

The CI will submit a final report to the required authorities (REC/MHRA) with the results, including any publications within one year of the end of the trial. Results will be uploaded to the ISRCTN trial registry and EudraCT.

The study was independently peer reviewed as part of the funding application to the NIHR.

7.3 Trial Registration

The trial will be registered with EudraCT and ISRCTN Registry prior to submission for approvals to commence the trial.

7.4 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

The sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design and management of the research protocol.

7.6 Trial timetable and milestones

	Month	Recruitment
Grant activation 13/01/2020		
Set-up	1-10	n/a
Pilot study	11-16	84
Paramedic Training	8-16	n/a
Main Trial Recruitment	17-26	362
Follow up	13-32	n/a
Analysis	32-37	n/a

7.7 Administration

The trial coordination will be based at WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The TSC, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The membership of the TSC is shown on page 6.

7.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on page 7.

DMC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

7.11 Essential Documentation

A Trial Master File will be set up according to Warwick SOPs and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files and Pharmacy Files to all recruiting centres involved in the trial.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

We will conduct a full Risk Assessment in accordance with Warwick SOPs and a monitoring plan will be developed which may include on-site visits.

9. PATIENT AND PUBLIC INVOLVMENT (PPI)

Patient and public involvement is embedded into this research. Our co-applicant Mr Duncan Buckley has personal experience of severe poly-trauma, including many analgesic strategies to manage pain, across different health care settings, over a long period of time. He has contributed to the development of this proposal from the outset and will be a core member of the research team. We also presented our proposal to the After Trauma PPI Group in London who are supportive of our proposal. Further PPI input will be provided through independent membership of the Trial Steering Committee

Our PPI group will be led by Mr Buckley. They will collaborate on study design, study materials and trial conduct. The PPI group will comment and advise the research team on findings, help to formulate recommendations and advise on design and implementation of the dissemination strategy.

We will follow INVOLVE best practice guidance in our approach. We will meet with the PPI group at the start of the study and regularly thereafter to enable full involvement through the trial and have included funds to support this. We will work with our PPI group to ensure that we are all clear about expectations and jointly agree a role description, terms of reference and organisational responsibilities including payments. Our named PPI lead Buckley (co-investigator) and the research team are wholeheartedly committed to meaningful engagement and collaboration throughout the project. We will provide members of the PPI group with training and support through informal mentorship with experienced PPI and formal training through our CRN PPI group. The PPI group will help keep patients and public informed through the progress of the trial and lead the dissemination of the trial findings to lay persons.

10. DISSEMINATION AND PUBLICATION

The approach will be informed by WCTU SOP 22 'Publication & Dissemination'.

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The success of the trial depends on the collaboration ambulance services, paramedics and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

Our dissemination strategy will target policy makers, commissioners, trauma networks, ambulance services, healthcare providers, academic audiences, patients and the public, charities and advocacy groups. It will include presentations at national and international conferences. We will submit publications to open access peer reviewed journals, develop a lay summary and infographic of the research findings. We will work with our patient and public partners to develop patient stories which effectively communicate key messages from the study. We will publicise via press releases to established media contacts and use our website, blog, Facebook page and Twitter feed to communicate our findings. Our research will support the development of an evidence-based pain management guideline for paramedics by NHS ambulance services. It will improve healthcare quality for patients with severe pain following trauma by engaging clinicians, patients, ambulance services and policy makers to provide better care, by reducing variation in practice and optimising the use of limited health resources.

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