APPLICATION SUMMARY INFORMATION

Programme Name	HTA
Funding Opportunity	Pre-hospital pain management
Call	18/44 Pre-hospital pain management
Host Organisation	University of Warwick

Research Title
A randomised controlled trial of Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma (PACKMaN)

Research Type	Primary Research
Proposed start date, end date (duration)	From: 01/01/2020 to: 31/12/2022 (36 months)
Total research costs (not including NHS Support & Treatment Costs)	£1,034,545.14
Total NHS support & treatment costs	£47,040.42
Total Non-NHS intervention costs	£0.00

LEAD APPLICANT DETAILS & CV

Details of Lead Applicant	Dr Michael Smyth
Job Position	Assistant Professor & Critical Care Paramedic
Department	Clinical Trials Division
Email / Phone	m.a.smyth@warwick.ac.uk 02476528039
Organisation	University of Warwick

Lead Applicant Information – Qualifications

Degree / professional qualification - subject	Awarding body - date of award
BSc (Hons) - Mathematics and computing	Open University - 01/10/2002
MSc - Health	University of Worcester - 01/10/2010
PhD - Health Sciences	University of Warwick - 01/11/2017

Lead Applicant Information – Recent Relevant Publications
Perkins, G. D., Ji, C., Deakin, C. D., Quinn, T., Nolan, J. P., Scomparin, C., Regan, S., Long, J., Slowther, A. & Pocock, H. & Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac

Lead Applicant Information – Recent Relevant Publications

arrest. New England Journal of Medicine 2018 August; 379:711-721.

Moore C, Bulger J, Morgan M, Driscoll T, Porter A, Islam S, Smyth M, Perkins G, Sewell B, Rainer T, Nanayakkara P, Okolie C, Allen S, Fegan G, Davies J, Foster T, Francis N, Smith FG, Ellis G, Shanahan T, Howe R, Snooks H. Prehospital recognition and antibiotics for 999 patients with sepsis: protocol for a feasibility study. Pilot and Feasibility Studies 2018 March;4:64.

Ji C, Lall R, Quinn T, Kaye C, Haywood K, Horton J, Gordon V, Deakin CD, Pocock H, Carson A, Smyth M, Rees N, Han K, Byers S, Brace-McDonnell S, Gates S, Perkins GD; PARAMEDIC trial Collaborators. Post-admission outcomes of participants in the PARAMEDIC trial: A cluster randomised trial of mechanical or manual chest compressions. Resuscitation. 2017 Sep;118:82-88.

Marti J, Hulme C, Ferreira Z, Nikolova S, Lall R, Kaye C, Smyth MA, Kelly C, Quinn T, Gates S, Deakin CD, Perkins GD. The cost-effectiveness of a mechanical compression device in out of hospital cardiac arrest. Resuscitation 2017 Aug;117:1-7.

Gates S, Lall R, Quinn T, Deakin CD, Cooke MW, Horton J, Lamb SE, Slowther AM, Woollard M, Carson A, Smyth M, Wilson K, Parcell G, Rosser A, Whitfield R, Williams A, Jones R, Pocock H, Brock N, Black JJ, Wright J, Han K, Shaw G, Blair L, Marti J, Hulme C, McCabe C, Nikolova S, Ferreira Z, Perkins GD. Prehospital randomised assessment of a mechanical compression device in out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised trial and economic evaluation. Health Technol Assess. 2017 Mar;21(11):1-176.

Fisher JD, Freeman K, Clarke A, Spurgeon P, Smyth M, Perkins GD, Sujan MA, Cooke MW. Patient Safety in Ambulance Services: a scoping review. Southampton (UK): NIHR Journals Library; 2015 May.

Lead Applicant Information – Research Grants Held

2018 Exploring and improving resuscitation decisions in out of hospital cardiac arrest (NIHR HS&DR) £683k - successful at stage 2 but not yet started.

2018 Major Trauma Triage Tool (NIHR HS&DR) (co-investigator) £901k

2017 Chief Investigators Fellowship (CRN West Midlands) (personal award) £230k

2017 Prehospital recognition and antibiotics in sepsis (PhRASe) RfPB Wales (co-investigator) £280k

2013 Clinical Doctoral Research Fellowship (NIHR TCC) (personal award) £440k

PREVIOUS APPLICATION HISTORY

Relevant NETS Programmes previous application information (within the last 3 years)

Other funders previous application information

APPLICATION BACKGROUND

Was this application submitted in response to a highlight notice?	No

Highlight Notice:

Previous Research Info

CLINICAL TRIALS

Clinical Trials Unit's (CTU) Participation

Is a Clinical Trials Unit involved with this research proposal?	Yes

Clinical Trials Unit's Information
Clinical Trials Unit Name: Warwick Clinical Trials Unit Registration Number if provided: 39 Is the CTU receiving CTU support funding from NIHR? Yes

If applicable, please describe how you have worked with a Clinical Trials Unit in developing you application and what support they will provide if funding is approved.
This trial has been planned in collaboration with a Clinical Trials Unit (both co-chief investigators and several co-applicants are based in a clinical trials unit). Clinical Trials Unit input has been essential for methodologic support, statistical plan, costing and project management. If funded, the CTU will continue to provide all thehe above functions. The management team all work in Warwick CTU.

If a Clinical Trials Unit is not being used, please explain why and who/what will be involved instead, if applicable to this application.

RESEARCH TEAM

Lead Applicant

Specify Lead Applicants role in research
Smyth and Perkins will jointly lead the project (as co-CI's) and ensure it is managed to time and within budget. Perkins (NIHR Senior Investigator) will mentor and support Smyth (past NIHR Fellow).

Lead Applicants % FTE Commitment	20%

Co-Applicants

Name	Position Held	Role	%FTE	Organisation	Agreed
Professor Gavin Perkins	Director	Co-Applicant co-chief investigator	10	University of Warwick Clinical Trials Unit	18/12/18
Associate Professor Joyce Yeung	Associate professor	Co-Applicant co-applicant	5	University of Warwick Clinical Trials Unit	11/12/18
Professor Stavros Petrou	Professor	Co-Applicant co-applicant	5	University of Warwick Clinical Trials Unit	11/12/18
Dr Felix Achana	Senior Research Fellow	Co-Applicant co-applicant	33	University of Warwick Clinical Trials Unit	11/12/18
Dr Gordon Fuller	Clinical Lecturer	Co-Applicant co-applicant	2.5	The University of Sheffield School of Health and Related Research (ScHARR)	14/01/19
Mr Duncan Buckley	none	Co-Applicant PPI representative	5	PPI none	12/12/18

Name	Position Held	Role	%FTE	Organisation	Agreed
Professor Ranjit Lall	Professor	Co-Applicant co-applicant (statistics)	10	University of Warwick Clinical Trials Division	04/01/19
Dr Alison Walker	Medical Director	Co-Applicant Local PI	5	West Midlands Ambulance Service NHS Foundation Trust Clinical directorate	05/01/19
Dr Julian Mark	Medical Director	Co-Applicant Principal Investigator	5	Yorkshire Ambulance Service NHS Trust Yorkshire Ambulance Service NHS Trust	16/01/19

Supporting Roles

Name	Position Held	Role	Organisation	Agreed
Dr Navdeep Bains	Assistant Director: Research Support and Contracts	Administrative Authority or Finance Office	University of Warwick Research & Impact Services	16/01/19
Dr helena white	Research Funding Officer	Administrative Contact	University of Warwick Research & Impact Services	14/01/19
Professor Gavin Perkins	professor	Administrative Contact	University of Warwick clinical trials unit	04/01/19
Professor Sudhesh Kumar	Dean	Head of Department	University of Warwick Warwick Medical School	14/01/19
Mrs Jane Prewett	Head of Research Governance	Sponsor	University of Warwick Research & Impact Services	16/01/19

Please declare any conflicts or potential conflicts of interest that you or your co-applicants may have in undertaking this research, including any relevant, non-personal & commercial interests that could be perceived as a conflict of interest.
Prof Perkins is a NIHR senior investigator Prof Petrou is a NIHR senior investigator

SCIENTIFIC ABSTRACT & PLAIN ENGLISH SUMMARY

Scientific Abstract

RESEARCH QUESTION
Is ketamine superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics?

BACKGROUND
Pain from severe trauma is poorly treated. NHS Paramedics have a limited formulary to treat severe pain. Ketamine may be an ideal prehospital drug due to its rapid onset of action, superior analgesic properties and safety. NICE identified the need to determine the clinical and cost effectiveness of ketamine against standard care (morphine).

AIM
To deliver a pragmatic, blinded, individually randomised, controlled trial, in two NHS Ambulance Trusts (informed by an internal pilot), which will determine the clinical and cost effectiveness of ketamine and morphine, among adult patients, with severe pain following trauma and who are attended by paramedics.

PRIMARY OBJECTIVE
To determine whether paramedic administered ketamine or morphine provides more effective pain relief for patients reporting severe pain following trauma.

SECONDARY OBJECTIVE
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.

DESIGN
Pragmatic, individually randomised, controlled, blinded trial, with economic evaluation.

SETTING
2 NHS Ambulance Services

POPULATION
Adult patients with severe pain following trauma, judged by the paramedic as requiring treatment with IV morphine.

INCLUSION CRITERIA
1. Age >16
2. Patient reports severe pain due to an acute traumatic injury
3. Vascular access obtained

EXCLUSION CRITERIA
1. Known or suspected pregnancy
2. Unable to articulate severity of pain using the 0-10 numerical rating scale
3. Ketamine or opioid analgesia received prior to screening
4. Contraindication to either ketamine or morphine
5. Patient declines participation

RANDOMISATION
Specially prepared, sequentially numbered treatment packs containing ampoules of either morphine or ketamine which are identical in appearance. Allocation will be concealed from study personnel, ambulance staff and patients.

Scientific Abstract

INTERVENTION
Ketamine hydrochloride.

COMPARATOR
Morphine sulphate.

PRIMARY OUTCOME
Sum of Pain Intensity Difference (SPID) score

SECONDARY OUTCOMES
Effectiveness of pain relieve / overall patient experience from randomisation to hospital arrival Side effects and adverse events
Resource use
Longer term outcomes
Cost effectiveness

SAMPLE SIZE
Using 1:1 randomisation, a power of 90%, significance level of 5% and a withdrawal/non-response rate of 2%, we require 526 subjects to detect a clinically relevant reduction of 1-point different (standard deviation=3.5) points on a 0-10 numeric pain scale.

TIMELINE
Months 0-6: study protocol, regulatory approvals, IMP manufacture; 7-16 paramedic training; 7-12 internal pilot phase; 13-24: main trial recruitment; 10-30: follow-up; 31-36: analysis and reporting

IMPACT AND DISSEMINATION:
Our research will support evidence-based pain management guidelines for use by paramedics within 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 and optimising limited health resources. We will disseminate the findings widely making use of infographic summaries, patient stories, publications, presentations, press releases and social med

Plain English Summary of Research

AIM

To decide if paramedics should use the pain killer ketamine, rather than morphine, to relieve severe pain in patients with injuries.

BACKGROUND

Pain after an injury is common. The strongest pain killer that UK paramedics routinely able to give is morphine. This can be slow to work and may cause side effects such as vomiting, drowsiness or low blood pressure. In some parts of the world (Australia, Canada and America) paramedics use a different pain killer called ketamine. Research from these countries tells us that ketamine might be better than morphine, but the research isn't good enough for us to be sure. We need to investigate if ketamine is suitable for use by paramedics working in UK ambulance services.

DESIGN

We will train paramedics to use ketamine safely and in procedures related to the trial. If an ambulance

Plain English Summary of Research

is called to a patient with severe pain after an injury, paramedics will check to see if the patient is suitable for our study.

We will consider patients who:

- Are 16 years of age or over
- Have suffered an injury which is causing severe pain
- Are able to have a strong pain killer administered through by injection

If the patient agree to take part, the paramedic will record how bad their pain is before treatment. The paramedic will then open a trial drug pack and administer the pain killer provided. Half of the drug packs will contain the pain killer, ketamine and half will contain the pain killer morphine. This will ensure an equal number of patients receive each treatment. The patient and paramedic will not know which drug is in the drug pack (sometimes called a double-blind study). This is important as it allows an unbiased assessment of how well each the drug works.

During the ambulance journey to hospital, if pain does not get better the paramedic will be able to give more of the pain killer. The paramedics will regularly monitor how well the pain killer is working. We will compare how good each of the pain killers worked to decide if ketamine is better than morphine for reducing severe pain after an injury.

PATIENT AND PUBLIC INVOLVEMENT

One of our research team is a member of the public who suffered serious injuries and has experience of many different pain treatments. In the past he has worked with other patients to help improve research in this area. He will work with us to guide the research and make sure it is focused on what is important to patients. He will help design, interpret and communicate our research and will play an important role in developing the final recommendations for new treatment guidelines for paramedics.

DISSEMINATION

We will share the study findings with paramedics, patients and those responsible for organizing and funding NHS Ambulance Services. We will do this through publishing our findings in medical journals and present them at meetings for doctors, nurses, paramedics and patients. We will highlight key messages from the research through patient stories. We will develop an easy to understand infographic (picture) which summarises the study findings. We will distribute this and a trial summary widely using our networks, via the internet and social media.

CHANGES FROM FIRST STAGE

Changes From First Stage

1) CLARIFY AND JUSTIFY THE ECONOMIC EVALUATION

The NICE Major Trauma Guideline (NG39) identified “Is morphine clinically and cost effective compared with ketamine for first-line pharmacological pain management (in both pre-hospital and hospital settings) in patients with major trauma?” as a research priority.

Ketamine may increase resource use and costs if it causes excessive sedation or abnormal emergence.

Inadequate acute pain relief is associated with long term health sequelae.

Our economic evaluation will take the form of within-trial and model-based cost-effectiveness analyses, conducted from the perspective of the UK NHS and personal social services and will include the incremental cost per QALY gained associated with ketamine versus morphine use in prehospital analgesia following serious injury. Full information is provided in the detailed project description.

2) INTERNAL PILOT

The internal pilot will be six months duration. Challenging progression criteria based on recruitment per month per site are summarised in the detailed project description.

3) GENERALISABILITY

We have included a 2nd NHS Ambulance Service to increase generalisability of the research findings.

4) JUSTIFY RESTRICTION TO TRAUMA

a) The background information provided to support the Commissioning Brief which highlights the relief of severe pain caused by traumatic injuries as a major un-met health need.

b) NICE (Clinical Guideline 39) specifically the need for this trial in patients with major trauma.

c) Ketamine is contra-indicated or cautioned in several medical conditions which can cause pain (e.g. acute porphyria, acute coronary syndrome, hypertensive crisis). These conditions can be difficult to identify with confidence in the pre-hospital setting.

d) Pain related to traumatic injury is acute in onset. Including non-traumatic pain would increase the heterogeneity in response to acute analgesia. The study is not powered to allow for wide heterogeneity in response to treatment which could be seen across a range of non-traumatic conditions and acute exacerbations of chronic conditions.

5) CONTRAINDICATIONS

Contraindications will be drawn from the BNF and summary of product characteristics. Paramedics will

Changes From First Stage
be trained to recognise contraindications for both drugs and will be provided with an aide memoire checklist. 6) CONSENT PROCESS This has been revised to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and Amendment Regulations 2006 (2006/2984). 7) LESSONS FROM KETAMORPH TRIAL We include a summary of the key differences between our trial and KETAMORPH and an update on progress on page 5. 8) PREGNANCY Whilst neither ketamine or morhpine are contraindicated in pregnancy, as this is a CTIMP, pregnant patients will be excluded. We describe on page 14 what we will do if someone is enrolled who is later found to be pregnant. 9) CHRONIC PAIN We have provided further detail of how we will assess chronic pain, justified the timeframe for doing so and the method we will use. Please see page 11. 10) BREAKTHROUGH PAIN Rescue analgesia will be provided if the trial intervention does not alleviate pain (page 12) and captured as a trial outcome. If after initially effective relief of pain, pain recurs, additional doses of the trial intervention will be given and captured as outcomes (duration of pain relief, overall effectiveness measures)

PATIENT & PUBLIC INVOLVEMENT

Please describe how patient and the public have been involved in developing this proposal
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.

Please describe the ways in which patients and the public will be actively involved in the proposed research, including any training and support provided
Our study has been designed to ensure meaningful patient and public involvement is embedded throughout the project. Further PPI input will be provided through independent membership of the Trial Steering Committee (2 members). We will convene a PPI group at the start of the project and work with them through the project. This group will be led by our PPI co-applicant Mr Buckley. 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 work with the PPI group to get their input in to the overall study design, development of study materials analysis and interpretation of findings. The PPI group will help formulate recommendations, and advise on the content and mode of delivery of study outcomes to lay audiences. Their role in shaping the overall direction and output from the research is critical for ensuring our approach is sensitive to and grounded in the needs of the wider community that the research may influence. 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 (monthly initially and then 3 monthly) 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) will be readily accessible to the group. We will provide training and support through informal mentorship with experienced PPI and formal training through our CRN PPI group. General training and support will be provided through access to the University's UNTRAP PPI programme. Project specific training which is tailored to the relevant research packages will be provided by the research team. 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.

In rare cases where proposals do NOT involve patients and the public, clear justification must be provided
not applicable.

JUSTIFICATION OF COSTS

Justification of Costs

All costings have been calculated in accordance with the AcoRD guidelines. University costs were calculated using TRAC methodology.

POSTS AND SALARIES (250k per year)

We have worked hard to keep costs to a minimum, whilst providing sufficient resource to deliver the project on time and within budget. This will be a demanding CTIMP so we have selected a senior and experienced team which is reflected in the cost for co-investigators. Based on feedback at stage 1 we have increased the trial timeline from 30 to 36 months between outline and full application to allow for 6 month pilot and addition of a 2nd site which has increased costs by 15%. We have removed one of the trial management staff posts to try to mitigate the increase.

Co-investigators: Chief investigator (20% FTE), Co-chief investigator (10%), Co-applicant anaesthetist (5%), Co-applicant emergency medicine (2.5%), Senior statistician (5%), Junior statistician (40%), Senior Health economist (5%), junior health economist (33%), Ambulance Service PI (2 x 5%), Paramedic research fellow (2 x 50%)

Trial management staff: CTU manager (5%), Senior project manager (15%), Trial Manager (100%), Administrator (100%), QA manager (5%), QA monitor (7.5%), Programming (33%).

PATIENT AND PUBLIC INVOLVEMENT (17k)

PPI Co-applicant (5% FTE), PPI members (indicative costs for 10 members, 4 meetings per year, £ 25 per hour plus travel and subsistence).

TRAVEL AND SUBSISTENCE (7K per year)

To cover site visits by CI and trial staff, investigator meetings, research fellow travel, attendance at oversight meetings (TSC/DMC)

EQUIPMENT (1.5K)

Computer and software purchase

OTHER COSTS

Paramedic training in trial protocol (2 x 15k), Incentive for patient survey completion (£ 10 per patient), MHRA costs (3k), trial archiving (2k)

DRUG COSTS (227k)

Manufacture, stability testing, distribution, of blinded investigational medicinal products.

DETAILED BUDGET SUMMARY

Research Costs Required from Funder

	Direct costs	Indirect costs	Total costs	% Costs paid by NIHR	Amount requested
Total Higher Education Institution Costs	641,615.07	208,329.21	849,944.28	80%	679,955.42
Total NHS Costs	224,904.00		224,904.00	100%	224,904.00
Total Commercial Costs	10,365.72	119,320.00	129,685.72	100%	129,685.72
Total Other Partnership Organisation Costs			.00	100%	.00

Total Research Costs Required from Funder	**£1,034,545.14**

Total NHS Support & Treatment Costs / (Savings)

	Total costs
NHS Support Costs Required from Networks	£8,028.00
NHS Treatment Costs Requested from the NHS	£62,708.40
Total NHS Support & Treatment Costs / (Savings)	£47,040.42

Total Funding Required

	Amount requested
Total Research Costs Requested (not including NHS Support & Treatment Costs)	£1,034,545.14
NHS Support & Treatment Costs / (Savings)	£47,040.42
Total Cost of Research (Research + NHS costs)	**£1,081,585.56**

DETAILED BUDGET BREAKDOWN

Posts & Salaries – Summary

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Total Higher Education Institution Costs	£147,641.36	£163,456.67	£157,123.62							
Total NHS Research Costs	£60,923.00	£61,663.00	£62,938.00							
Total Commercial Costs										
Total Other Partnership Organisation Costs										
Total NIHR Awarded Costs	£208,564.36	£225,119.67	£220,061.62							

Finance costs (summary)

Travel, Subsistence & Dissemination Costs - Summary

	Total Costs
Total Higher Education Institution Costs	£16,960.00
Total NHS Costs	£0.00

Total Commercial Costs	£0.00
Total Other Partnership Organisation Costs	£0.00
Total NIHR Awarded Costs	£16,960.00

Equipment - Summary

	Total Costs
Total Higher Education Institution Costs	£1,248.00
Total NHS Costs	£0.00
Total Commercial Costs	£0.00
Total Other Partnership Organisation Costs	£0.00
Total NIHR Awarded Costs	£1,248.00

Consumables - Summary

	Total Costs
Total Higher Education Institution Costs	£0.00
Total NHS Costs	£0.00
Total Commercial Costs	£0.00
Total Other Partnership Organisation Costs	£0.00

Patient and Public Involvement Costs - Summary

	Total Costs
Total Higher Education Institution Costs	£9,600.00
Total NHS Costs	£0.00
Total Commercial Costs	£0.00
Total Other Partnership Organisation Costs	£0.00
Total NIHR Awarded Costs	£9,600.00

Other Direct Costs - Summary

	Total Costs
Total Higher Education Institution Costs	£17,262.40
Total NHS Costs	£39,380.00

Total Commercial Costs	£10,365.72
Total Other Partnership Organisation Costs	£0.00
Total NIHR Awarded Costs	£67,008.12

HEI Indirect Costs – Summary

Estates Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
University of Warwick Total: £22,996.53	£7,665.51	£7,665.51	£7,665.51							
University of Sheffield Total: £487.00	£19.00	£234.00	£234.00							
Total:	£7,684.51	£7,899.51	£7,899.51							
Total NIHR Awarded Costs:	£6,147.61	£6,319.61	£6,319.61							

Other Indirect Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
University of Warwick Total: £182,233.68	£60,744.56	£60,744.56	£60,744.56							
University of Sheffield Total: £2,612.00	£106.00	£1,253.00	£1,253.00							
Total:	£60,850.56	£61,997.56	£61,997.56							
Total NIHR Awarded Costs:	£48,680.45	£49,598.05	£49,598.05							

Commercial and Other Partnership Organisation Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10

Travel, Subsistence & Dissemination Costs – Details

Journey Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Travel to UK Conference x 2 people HEI Total: £360.00	£360.00	£0.00	£0.00							
Overseas Conference travel x 1 person HEI Total: £800.00	£800.00	£0.00	£0.00							
Steering Committee Meeting Travel HEI Total: £5,600.00	£1,600.00	£2,400.00	£1,600.00							
DMEC Travel HEI Total: £5,600.00	£1,600.00	£2,400.00	£1,600.00							
MREC Travel HEI Total: £100.00	£100.00	£0.00	£0.00							
PI Site Visits HEI Total: £300.00	£100.00	£100.00	£100.00							
Total:	£4,560.00	£4,900.00	£3,300.00							
Total NIHR Awarded Costs:	£3,648.00	£3,920.00	£2,640.00							

Subsistence

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Subsistence (Incl Hotels) UK Conference x 2 people HEI Total: £500.00	£500.00	£0.00	£0.00							
Overseas Conference subsistence (incl hotels) x 1 person HEI Total: £700.00	£700.00	£0.00	£0.00							
Total:	£1,200.00	£0.00	£0.00							
Total NIHR Awarded Costs:	£960.00	£0.00	£0.00							

Dissemination Costs - Conference

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
UK Conference fees x 2 people HEI Total: £740.00	£740.00	£0.00	£0.00							
Overseas Conference fees x 1 person HEI Total: £500.00	£500.00	£0.00	£0.00							
Total:	£1,240.00	£0.00	£0.00							

Total NIHR Awarded Costs:	£992.00	£0.00	£0.00							

Dissemination Costs - Open Access

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Open Access Publication Charges HEI Total: £6,000.00	£0.00	£2,000.00	£4,000.00							
Total:	£0.00	£2,000.00	£4,000.00							
Total NIHR Awarded Costs:	£0.00	£1,600.00	£3,200.00							

Dissemination Costs - Other

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10

Equipment – Details

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Laptop x 2 Exc. VAT: £1,300.00 Reclaimed: No HEI Total: £1,560.00	£1,560.00	£0.00	£0.00							

Total:	£1,560.00	£0.00	£0.00							
Total NIHR Awarded Costs:	£1,248.00	£0.00	£0.00							

Consumables – Details

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10

Patient and Public Involvement Costs – Details

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
10 PPI members to meet 12 times over the duration of the project at an indicate cost of £ 25 per hour (average 2 hour meeting, 1 hour preparation) @ 9k; travel (1.2k), subsistence (1.2k), training (£600) HEI Total: £12,000.00	£4,000.00	£4,000.00	£4,000.00							

Total:	£4,000.00	£4,000.00	£4,000.00							
Total NIHR Awarded Costs:	£3,200.00	£3,200.00	£3,200.00							

Other Direct Costs – Details

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Paramedic Training Payment - West Midlands NHS Total: £15,000.00	£15,000.00	£0.00	£0.00							
Paramedic Training Payment - Yorkshire NHS Total: £15,000.00	£15,000.00	£0.00	£0.00							
CRF completion NHS Total: £9,380.00	£9,380.00	£0.00	£0.00							
Steering Committee Refreshments HEI Total: £871.50	£249.00	£373.50	£249.00							
DMEC Refreshments HEI Total: £871.50	£249.00	£373.50	£249.00							
Printing costs HEI Total: £500.00	£250.00	£250.00	£0.00							

Survey form completion by patients HEI Total: £13,200.00	£13,200.00	£0.00	£0.00							
Advertising HEI Total: £500.00	£500.00	£0.00	£0.00							
MHRA costs HEI Total: £3,310.00	£3,310.00	£0.00	£0.00							
Archiving costs HEI Total: £2,000.00	£0.00	£0.00	£2,000.00							
Licence fee to use Brief Pain Index - Short Form as an outcome measure. HEI Total: £325.00	£325.00	£0.00	£0.00							
Midazolam Drug Costs 5mg in 5ml x 150 ampoules of midazolam, blinding/manufacturing not needed. £6 per unit Commercial Total: £1,080.00	£1,080.00	£0.00	£0.00							
drug pouches WMAS Commercial Total: £4,642.86	£4,642.86	£0.00	£0.00							
drug pouches YAS Commercial Total: £4,642.86	£4,642.86	£0.00	£0.00							

Total:	£67,828.72	£997.00	£2,498.00							
Total NIHR Awarded Costs:	£64,212.12	£797.60	£1,998.40							

NHS Support and Treatment Costs

Have you discussed and agreed these support costs with The Lead Network?	Yes
Have you discussed and agreed these treatment costs with The Lead Trust?	Yes
Is the patient care being provided different from the usual treatment for the condition?	Yes

NHS Support Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
participant identification, participant consent £0.00 Total: £8,028.00	£2,676.00	£5,352.00	£0.00							
Total:	£2,676.00	£5,352.00	£0.00							

NHS Treatment Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
NHS Treatment Costs as taken from SoECAT £0.00 Total: £62,708.40	£20,902.80	£41,805.60	£0.00							

Total:	£20,902.80	£41,805.60	£0.00							

Usual Treatment Costs

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Usual Treatment Cost as taken from SoECAT £0.00 Total: £23,695.98	£7,899.00	£15,796.98	£0.00							
Total:	£7,899.00	£15,796.98	£0.00							

Excess Treatment Costs / (Savings)

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Excess Treatment Cost: £39,012.42	£13,003.80	£26,008.62	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00

MANAGEMENT & GOVERNANCE

Is Clinical Trial Authorisation required?	Yes
Does your project require ethics approval?	Yes
If yes, has ethics approval already been obtained?	No

UPLOADS

The following pages contain the following uploads:

Upload Name
Cover Letter (Response to Feedback)
Detailed Research Plan (Tracked Changes)
Detailed Research Plan (Final Clean Version)
Flowchart
References
Supporting Letter (CTU)
Additional Documentation

21 June 2019

Lynn Kerridge
Chief Executive Officer, NETSCC
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton
Alpha House, Enterprise Road
Southampton
SO16 7NS

Dear Mrs Kerridge

Ref: NIHR 128086 A randomised controlled trial of paramedic analgesia comparing ketamine and morphine in trauma (PACKMaN)

Thank you for your letter of 26th April advising that the Board has recommended funding of the above named project, subject to a satisfactory response to points raised in the award letter. We thank the Board and secretariat for their helpful comments on our proposal.

We provide a detailed response to the Board and finance queries raised below.

The applicants should adjust the sample size to allow for a smaller SD in line with other similar trials and also allow for a more realistic higher rate of withdrawal. Any reduction in sample size should be reflected in a corresponding reduction in costs.

As recommended by the board, we have adjusted our SD and recalculated our sample size allowing for a higher rate of withdrawal. We now adopt a SD of 3.0 (reduced from 3.5) as this is the most commonly reported SD in published studies. We have increased our withdrawal rate from 2% to 15% as this was the largest reported withdrawal rate in published prehospital studies of ketamine for analgesic purposes. We have therefore amended our sample size calculation as follows:

"We calculate a sample of 446 subjects is required, recruiting 223 to each arm of the study to detect a 1 point difference (0 – 10 NRS), in effectiveness between morphine and ketamine. This estimation assumes 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%."

The overall research costs for the proposal have reduced from £1,123,179.42 to £ 1,027,773.14.

The Committee had concerns about the consent process and would like the applicants to monitor the feasibility and acceptability of the consent process during the pilot phase.

We note the concern of the board in relation to our proposed consent process. In collaboration with our Ambulance Trust partners and PPI collaborators we will ensure robust monitoring of the consent process is in place during the pilot phase to ensure all our obligations to patients are met, and that the consent process is acceptable to participants.

The Committee was unconvinced by the value of the long term economic model and justification is needed.

In designing the proposed economic evaluation, we were cognisant that a within-trial economic evaluation might not be conducted over a long enough time horizon to capture differences in relevant

economic outcomes[1]. We were guided by external evidence suggesting that inadequate early pain management may be linked to chronic pain, anxiety, depression and post traumatic distress disorder over the longer term (protocol references 5, 6, 55, 56). Under these circumstances, a decision analytic modelling economic evaluation would allow us to simulate economic costs and consequences associated with post-injury disability over a longer term time horizon, as well as incorporate relevant evidence from external trials, meta-analyses, and observational studies where these are, or become available.

We recognise that the need for long-term extrapolation of cost-effectiveness hinges on biologically plausible mechanisms linking early pain management with long-term clinical sequelae. Given that published evidence from longitudinal studies is limited and equivocal in this regard[2], we are happy to limit the proposed economic evaluation to a within-trial analysis that mirrors the time horizon for the trial, namely extending to six months post-randomisation. We will continue to monitor external evidence and only develop a longer-term economic model if robust evidence emerges from longitudinal studies clearly establishing the adverse longer-term effects of inadequate early pain management.

The project timescales seem over ambitious, and the applicants should consider increasing the length of the set-up phase without an increase in costs.

We have extended our set-up phase from 6 months to 8 months without increasing costs. A reduction in sample size means we will be able to reach our recruitment target 2 months sooner than previously calculated. This period, previously allotted to recruitment, will instead be used to extend our set-up phase.

Patient and public involvement should be strengthened to include a broader patient representation and should include the younger group and women.

We will broaden our patient representation as suggested to include the younger group and women. We have not yet identified individuals to collaborate but we have started the process to do so. In the first instance we have opened a dialogue with Midlands Air Ambulance with a view to identifying past patients who now volunteer for the charity. From these volunteers we will invite a younger person and a female representative to collaborate on our study. Should this approach fail we will reach out to our ambulance service partners and colleagues conducting other pain related studies to identify suitable individuals.

Finance Feedback

Please provide the salary details for Alison Walker, the Research Paramedics and the Local Co-Investigator.

Annual salary details, including pension and national insurance contributions, are as follows:

Dr Alison Walker: £148,000
Dr Julian Mark: £148,000
Band 6 Research paramedic: £48,940

[1] Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? *Health Economics* 2006:15(7):677-87.

[2] Jennings PA, Cameron P, et al. Long-term pain prevalence and health-related quality of life outcomes for patients enrolled in a ketamine versus morphine for prehospital traumatic pain randomised controlled trial. Emergency Medicine Journal 2014;31:840-3.

Please provide more information on the paramedic training. If there is training in the administration of the IMP that would continue if the IMP became standard care, we would expect a proportion of the training cost to be an NHS Treatment Cost.

Training of clinicians will take 3 hours. One hour will be a research cost addressing the rationale for the trial, consent processes in the context of a CTIMP, trial related procedures (assessment of eligibility, drug monitoring tracking, measuring and recording trial outcomes, serious adverse event reporting). An additional 2 hours training (included as treatment costs) will provide information about the use of ketamine (and midazolam which is required to manage potential side effects) as a pain killer in traumatic injury.

Please provide more information on the drug costs, including a quote. We do not expect there to be any costs for drug costs included as research cost as these should be NHS Treatment Costs. Costs for over-labelling, distribution, etc. can remain as a research cost.

PACKMaN is a blinded randomised controlled trial. Our supplier will be over-labelling morphine ampoules (10mg in 1ml) as suggested. However, ketamine is not available in the presentation required for this study (ampoule of 15mg in 1ml). The smallest available presentation is a vial of 200mg in 20ml. As a consequence ketamine ampoules need to be manufactured and a research cost will be incurred.

We enclose a formal quotation for IMP from our supplier MODEPHARMA, and have updated the finance section of our application to reflect these costs.

The costs for the drugs themselves, are included as a treatment costs.

We expect there to be NHS Support costs included for the consenting of patients.

We have included time to consent patients by research paramedics as a NHS support cost in our SoECAT.

Costs for the Ketamine should be included for 50% of patients (263) in NHS Treatment Costs section of the form.

We have included costs of ketamine and midazolam (must be available to manage emergence phenomena should they occur) for 223 patients (revised sample size) in our SoECAT.

Costs for the Morphine should be included in the Usual Treatment Costs section of the form for 263 patients.

We have included costs of morphine and naloxone (must be available when morphine is administered by paramedics) for 223 patients (revised sample size) in our SoECAT.

You will need to complete and submit a SoECAT for this application. Please approach the network regarding this.

We have completed and submitted a SoECAT form.

Intellectual Property (IP) Feedback
Please clarify what third party rights exist in relation to background IP. If there are none then please inform us as this means there will be no requirement for schedule C in the contract. If third party rights exist in relation to background IP please provide proposed wording for the following.

There are no background IP concerns in relation to this project .

It is NIHR's starting position that all arising foreground IP shall vest with the contractor. If you wish NIHR to consider alternative ownership arrangements then please provide your proposed wording so it can be reviewed and, if approved, will replace the standard wording to Schedule D.

We propose that foreground IP will be owned by the University of Warwick and that IP considerations shall be subject to the NIHR terms and conditions which will take precedence over any collaboration agreements put in place between the organisations involved in the study.

If you have not already done so, I would strongly encourage you to discuss the above points with the appropriate department at your University/ Trust e.g. Research Office, Technology Transfer Office, Contracts Office etc. Please provide me with the contact details for your contact(s) in these departments so that I can copy them in to future correspondence when appropriate.

Ms Parminder Matharu
Research funding officer
Research and Impact Services
University of Warwick
024765 22887
Parminder.Matharu@warwick.ac.uk

Consider fully the issue of intellectual property, and provide details of background IP involved in the study, and what foreground IP will be generated and how this will be managed to maximise patient benefit.

We will not be utilising any background IP in this study. Foreground IP will include training materials and publications arising from the study. We have detailed our approach to the dissemination of training materials, publications and other outputs within our application.

Please provide any agreements that might be put in place with the manufacturer and distributor of the drugs to the HTA Programme prior to signature. Please advise of the potential timeline for these to be submitted.

We have included the formal quote from MODEPHARMA. Section 7 includes details of the expected timelines.

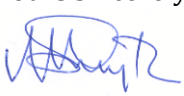
Please confirm that licences are in place to use any outcome measurement tools.

We will be utilising the following outcome measures:

1. Sum of Pain Intensity Difference (SPID) - no licence required
2. Total Pain Relief score (TOTPAR) - no licence required
3. EQ-5D-5L – licence in place
4. BPI-SF - $300 licence fee and $100 processing fee (total $400) payable. We have placed a purchase order (728-20190524) to utilise this symptom assessment tool

We hope that our response to your feedback is well received.

Yours sincerely



Dr Mike Smyth PhD
Assistant professor Emergency and Critical Care,
Warwick Clinical Trials Unit

On behalf of co-investigator team

Project reference: NIHR128086

1 FULL TITLE OF PROJECT

Prehospital analgesia comparing ketamine and morphine in trauma. A randomised controlled trial and economic evaluation

2 SUMMARY OF RESEARCH

Research question: Is ketamine superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics?

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

Aims and objectives:

Aim: To deliver a pragmatic, blinded, individually randomised, controlled trial, in two NHS Ambulance Trusts (informed by an internal pilot), which will determine the clinical and cost effectiveness of ketamine and morphine, among adult patients, with severe pain following trauma and who are attended by paramedics.

Primary objective: To determine whether paramedic administered ketamine or morphine provides more effective pain relief for patients reporting severe pain following trauma.

Secondary objectives: 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.

Design: Pragmatic, individually randomised, controlled, blinded, trial, with economic evaluation.

Setting:

- West Midlands Ambulance Service University NHS Foundation Trust which serves a population of 5.2 million over 5 counties and 7 cities.
- Yorkshire Ambulance Service NHS Trust which serves a population of 8.6 million

Population: Adult patients (age ≥16 years) with severe pain following trauma, judged by the paramedic as requiring treatment with IV morphine or equivalent.

Inclusion criteria:

1. Age >16
2. Patient reports severe pain due to an acute traumatic injury
3. Vascular access obtained

Exclusion criteria:

1. Known or suspected pregnancy
2. Unable to articulate severity of pain using the 0-10 numerical rating scale
3. Ketamine or opioid analgesia received prior to screening
4. Contraindication to either ketamine or morphine
5. Patient declines participation

Randomisation: Specially prepared, sequentially numbered treatment packs containing ampoules of either morphine or ketamine which are identical in appearance. Allocation will be concealed from study personnel, ambulance staff and patients.

Intervention: Ketamine hydrochloride.

Project reference: NIHR128086

Comparator: Morphine sulphate.

Primary outcome:

Sum of Pain Intensity Difference (SPID) score. The SPID is a patient focused measurement which combines the magnitude and duration of pain relief.

Secondary outcomes:

Effectiveness of pain relieve /overall patient experience
Side effects and adverse events
Resource use
Longer term outcomes
Cost effectiveness

Sample size: Using 1:1 randomisation, a power of 90%, significance level of 5% and a withdrawal/nonresponse rate of 15%, we require 446 subjects to detect a clinically relevant reduction of 1-point different (standard deviation=3.0) points on a 0-10 numeric pain scale.

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Timeline:
Month 0-8: study protocol, regulatory approvals, IMP manufacture
Month 9-18: paramedic training
Month 9-14: internal pilot phase
Month 15-24: main trial recruitment
Month 12-30: follow-up
Month 31-36: analysis and reporting

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Anticipated impact and dissemination: 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.

3 BACKGROUND AND RATIONALE

At least 70% of Ambulance calls are related to patients experiencing pain.[1] Observational studies provide evidence that current treatments leave many patients with in-adequate 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. The World Health Organisation declared in 2004 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

posttraumatic 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 approaches

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

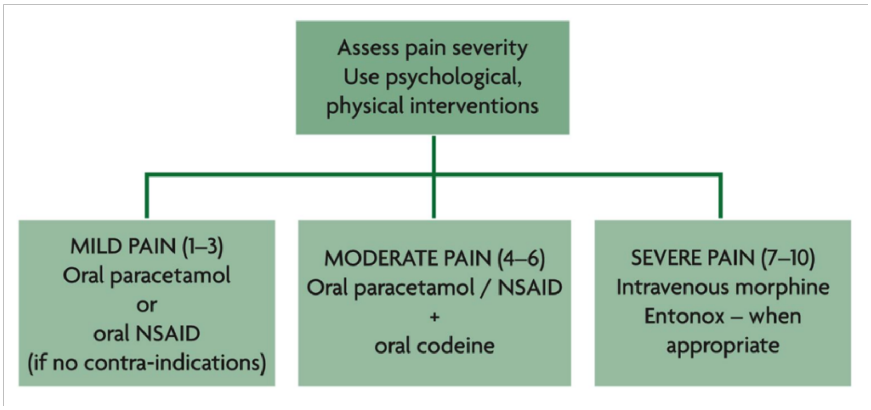

Figure 1 Approach to prehospital pain management

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 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. Seriouas adverse outcomes have not been reported even though overdoses of 5 to 100 times the intended dose have been inadvertently administered.[27] Due to it's 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.

Current practice

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. Assessment of the certainty of evidence using the GRADE recommendations, the 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 randomized 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 totaling 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 2 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 generalizability 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 clinicians willingness to enroll 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.

3a WHY IS THIS RESEARCH NEEDED NOW?

i. *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.

ii. *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.

iii. *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.

iv. *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.

v. *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.

vi. *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]

4 AIMS AND OBJECTIVES

Overall aim:

To deliver a pragmatic, blinded, individually randomised, controlled trial, in two NHS Ambulance Trusts, informed by an internal pilot), which will determine the clinical and cost effectiveness of ketamine and morphine, among adult patients, with severe pain following trauma and who are attended by paramedics.

Primary Objective:

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, 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.

Secondary objectives:

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.

Specifically we will assess:

1. Effectiveness of pain relief overall patient experience from randomisation to arrival at hospital
   a. Total Pain Relief (TOTPAR) score (using a 0-10 numerical rating scale)
   b. Time to effective analgesia, duration of analgesia
   c. Requirement for rescue analgesia
   d. Proportion of patients with a pain intensity score below 4/10 (0-10 numerical rating scale) on arrival at hospital
   e. Patient Global Impression of Change on arrival at hospital
2. Incidence of side effects and adverse events
   a. Airway: vomiting, aspiration, advanced airway management
   b. Respiratory: desaturation, need for ventilatory support
   c. Cardiovascular: arrhythmia, hypotension and hypertension
   d. Neurologic: sedation, excitatory movements, adverse behavioural reactions
   e. Other: allergic reaction, serious unexpected serious adverse reactions
3. Resource use
   a. Ambulance job cycle time (scene arrival to arrival at hospital)
   b. CT scan use
   c. Hospital or ICU admission
   d. Length of stay ED, ICU, Hospital
4. Longer term outcomes
   a. Chronic pain using BPI-SF at 3 months from randomisation
   b. Health-related quality of life at 3 and 6 months from randomisation EQ-5D-5L
5. Cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained using EQ-5D 5L (at hospital discharge, 3 and 6 months)

5 RESEARCH PLAN / METHODS

Trial design:

Our study is designed to address the research gap identified by the NICE Major Trauma Guideline (NG39). Specifically, *"Is morphine clinically and cost effective compared with ketamine for first-line pharmacological pain management (in both pre-hospital and hospital settings) in patients with major trauma?"* This study is a pragmatic, double blind, randomised controlled trial and economic evaluation, with an internal pilot and blinded assessment of outcomes up to 6 months after randomisation. In PICO terms:

Project reference: NIHR128086

Population:	Adult patients reporting severe pain following acute traumatic injury, who are able to express a pain intensity score utilising a 0-10 numeric rating scale (NRS).
Intervention:	Intravenous ketamine hydrochloride
Comparator:	Intravenous morphine sulphate
Outcomes:	Clinical and cost-effectiveness outcomes up to 6 months

Research question*:*

Is ketamine superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics?

Study:

Internal pilot study:

The main study will be preceded by a six month internal pilot. The progression of the pilot is informed by recently published best practice guidelines.[65] We anticipate that by six months we will recruit a minimum of 48 patients (24 per treatment arm, 9% of the total sample).[65] The pilot will take place in two ambulance hubs, one from each participating ambulance service. The pilot will be used to confirm training, recruitment, compliance, data capture and follow-up assessments.

Our recruitment rate is anticipated to be 4 patients, per 50 participating ambulance paramedics, per month open to recruitment. Success criteria for recruitment will be based on the traffic light system:

Go:	75-100% recruitment: progress to main trial following a review of screening logs and protocol. Any barriers for recruitment will be addressed
Amend:	50-75% recruitment: progress to main trial with additional sites being recruited as well as a screening log and protocol review
Stop:	less than 50% recruitment: the decision to progress will be made by the Trial Steering Committee in association with the HTA secretariat. Protocol compliance and the completeness of follow-up data will be reviewed by the DMC and TSC, noting that six months follow-up data will not be completed at the end of the pilot

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 deviations, violations, 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.

Main study:

The remaining sample of 446 patients (223 per treatment arm) will be enrolled into the main study. The main study will take place in two English ambulance services which have a proven track record of successful participation in clinical trials. The main study will recruit over a period of 12 months.

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We will undertake a process evaluation and assess the implementation of trial procedures e.g. training, auditing screening logs, recruitment, reasons for exclusion and protocol compliance. Any indication of poor compliance will trigger additional training for participating paramedics. We will hold monthly teleconference meetings with the participating ambulance trusts to identify any recruitment issues and any difficulty with implementing the trial protocol.

We will provide feedback periodically to participating ambulance trusts based on performance monitoring described above and, if required, refine educational packages to target any specific barriers to recruitment.

Consent

We have carefully considered the approach to consent in the context of advice from our patient / public representatives, a review of the HRA guidance in relation to Clinical Trials of Investigational Medicinal Products (CTIMPS) in an emergency setting. We have applied our teams and other research teams previous experience of research in this setting. As we develop the full trial protocol, we will have further opportunities for input from our patient and public collaborators.

The clinical trials regulations require that for consent to be considered legal, it must be provided in writing, the patient must have capacity, it must be given voluntarily without undue influence, and given by someone who has been adequately informed and a fair choice.

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 due to the nature of their injuries (e.g. broken arm) or location (e.g. trapped in the wreckage of a car). Withholding pain relief to obtain written informed consent has in some settings been considered coercion and is not regarded as best practice. It is our assessment that few patients with acute, severe traumatic pain will have sufficient physical and mental capacity to provide written informed consent.

The urgency with which treatment for acute severe pain must be provided precludes it being practical to obtain written informed consent from a personal legal representative as to do so would delay treating the patients pain. The enrolling paramedic will not have timely access to a professional legal representative making such an approach impractical.

We will therefore seek approval from the Research Ethics Committee to enrol patients in to the clinical trial using the provisions within the Clinical Trials Regulations (2006, No 2984) for adult patients who lack capacity on the basis that:

- The patient is incapacitated
- Treatment needs to be given urgently
- It is necessary to take urgent action to administer the drug for the purposes of the trial
- It is not reasonably practicable to obtain consent from a legal representative
- The procedure is approved by a NHS Research Ethics Committee
- Consent is sought from a legal representative as soon as possible

Consent process:

Prior to enrolment, the paramedic will provide brief verbal information to the patient (and / or personal legal representative) about the intention to enrol the patient in the trial and confirm their willingness in principle to participate. If the patient or personal legal representative indicate any objection, standard care will be provided without prejudice.

Once the initial emergency has passed, and the patients pain is under control, the enrolling paramedic will assess the patients capacity to determine if they are able to make an informed decision to continue in the trial. The paramedic will seek consent to continue participation in the trial as follows:

Patient has capacity to consent - Where the paramedic assesses that the patient has capacity, then they will provide written information (participant information sheet) regarding the study and seek written, informed consent from the patient to continue in the trial.

Patient lacks capacity to consent - Where the paramedic assesses the patient lacks capacity, then they will seek consent from a personal legal representative provided this will not unduly delay the provision of continuing clinical care. 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. Research staff will continue with attempts to obtain written informed consent from the participant at each point of contact.

Patient or legal representative withdraws consent - If at any point following enrolment the patient (or their legal representative) indicates that they no longer wish to participate in the trial then no further study related treatment will be provided, and usual care will provided. All non-identifiable data up to the point of withdrawal will be retained in accordance with the trials regulations. No further data collection will be conducted from this point onwards.

This approach is consistent with the EU Clinical Trials Directive[69] and the soon to be implemented EU Clinical Trials Regulations.[70] We will additionally collaborate with our Ambulance Trust partners and PPI collaborators to robustly monitor the consent process during the pilot phase to ensure all our obligations to patients are met, and that the consent process is acceptable to participants. We will confirm these consent arrangements with an independent NHS Research Ethics Committee (REC) prior to commencement of the trial.

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Randomisation and blinding:

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 study statistician. 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.

Outcome measures and justification:

Outcome measures have been selected to address the commissioning brief, namely to evaluate a potentially sustainable intervention to improve the management of acute pain in the pre-hospital setting.

Outcome	Trial outcome	Rationale
Primary outcome	Sum of Pain Intensity Difference	Recommended by IMMPACT and EMA

Secondary outcomes	Total Pain Relief (TOTPAR)	Recommended by IMMPACT and EMA
	Time to effective analgesia and duration of analgesia	Recommended by IMMPACT and EMA
	Proportion of patients requiring rescue analgesia during prehospital care	Advocated by IMMPACT recommendations
	Proportion of patients with a pain <4/10 on arrival at hospital	Advocated by IMMPACT recommendations
	Patient Global Impression of Change	Recommended by IMMPACT and EMA
	Incidence of adverse events and serious adverse events	Advocated by IMMPACT recommendations
	Resource use	To quantify the impact on the emergency care pathway
	Long term outcomes – HRQL and chronic pain	Recommended by IMMPACT and EMA and referred to in the commissioning brief
Cost effectiveness	Cost-effectiveness from the perspective of NHS and personal social services	Need identified by NICE (NG39)

IMMPACT - Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations.[63]
EMA – European Medicines Agency.[64]

Primary outcome:

As advocated by IMMPACT core outcome recommendations, our primary outcome is the Sum of Pain Intensity Difference (SPID). The SPID is a patient focused measurement which combines the magnitude and duration of relief in a single score.

Sum of Pain Intensity Difference is calculated using the pain-intensity difference (PID). The PID is the difference between current pain intensity (0-10 NRS) and baseline pain intensity (0-10 NRS). Baseline pain intensity is the pain intensity (0-10 NRS), before analgesia is administered. Pain intensity will be measured at 10 minute intervals from randomisation to arrival at hospital. SPID is the summation of the PID at each interval, weighted according to the amount of time since the previous PID assessment; it approximates the area under the curve for PID over time. The benefit of using SPID is that it takes into account individual differences in baseline pain intensity, improvements in pain intensity and time. SPID is also reported as a percentage of maximum possible SPID (%SPID). Maximum possible SPID is the value that would be achieved if the patient were pain free (NRS = 0) for the entire study period.

We have selected the 0-10 numerical rating scale in preference to other pain intensity scales as it is easily understood by participants, is easily translatable[63] and is currently used by NHS Ambulance Services.

Secondary outcomes:

As advocated by IMMPACT and EMA and our patient and public partner, our secondary outcomes will include:

1. Overall effectiveness of pain relief / patient experience from randomisation to hospital admission

   a) Total Pain Relief (TOTPAR), a summary measure that integrates serial assessments of a pain intensity over time (the prehospital interval). It is a time-weighted measure of total area under the pain relief curve.
   b) Time to effective analgesia, duration of analgesia.

c) Proportion of patients requiring rescue analgesia during prehospital care.
d) Proportion of patients with a pain intensive score below 4/10 on NRS on arrival at hospital
e) Patient Global Impression of Change at hospital. Patient focused outcome which assesses improvement and overall satisfaction with treatment—assessed by the seven-point Patient Global Impression of Change scale.[71]

2. Side effects and adverse events

a) Airway: vomiting, aspiration, advanced airway management
b) Respiratory: desaturation, need for ventilatory support
c) Cardiovascular: arrhythmia, hypotension and hypertension
d) Neurologic: sedation, excitatory movements, adverse behavioural reactions
e) Other: allergic reaction, serious unexpected serious adverse reactions

3. Resource use
a) Ambulance job cycle time (scene arrival to arrival at hospital)
b) CT scan use
c) Hospital or intensive care admission
d) Length of stay in emergency department, intensive care, hospital

4. Longer term outcomes
a) Chronic pain using BPI-SF at 3 months (see below)
b) Health-related quality of life at 3 months and 6 months using EQ-5D-5L

5. Cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained using EQ-5D 5L (at hospital discharge, 3 and 6 months)

We will assess chronic pain at 3 months post recruitment.[72] We will follow-up via telephone and use the Brief Pain Inventory – Short Form (BPI-SF).[73] The BPI-SF is an 11-item, pain-specific quality of life measure. It is split into two parts: a four item 'pain severity' domain and a seven-item 'pain interference' scale. It is reported as a total pain severity scale, though for the purposes of chronic pain, pain average is felt to be the most accurate representation of a person's pain.[73] The BPI-SF has been validated in chronic non-cancer patients and captures pertinent information including pain intensity, pain medications and patient reported interference on mood, sleep and physical function.[74] [75] It can be successfully completed via telephone.[76]

Health technology being assessed:

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.

Control: **morphine sulphate** *(10mg in 10ml)*
- Initial dose: 10ml (10mg) titrated to effect (2ml per minute for 5 minutes)
- Repeat dose: 2ml (2mg) (minimum of 5 minutes elapsed since last dose)
- Maximum cumulative dose: 20 ml (20mg)

Intervention: **ketamine hydrochloride** *(15mg in 10 ml)*
- Initial dose: 10ml (15mg) titrated to effect (2ml per minute for 5 minutes)
- Repeat dose: 2ml (3mg) (minimum of 5 minutes elapsed since last dose)
- Maximum cumulative dose: 20 ml (30mg)

If the patient weighs less that 50kg (actual or estimated), or if the paramedic providing treatment has concerns regarding patient frailty, then treatment should be adjusted. In such circumstances the paramedic will titrate the trial drug administering 1ml per minute over 10 minutes, rather than 2ml per minute over 5 minutes.

Slowing the rate at which the trial drug is administered will reduce the likelihood of a frail patient inadvertently receiving more drug than clinically required and lower the risk of adverse effects in this population.

Both morphine and ketamine have predictable side effects that may require subsequent treatment. Although rare (<5%), morphine sulphate may cause respiratory depression and ketamine hydrochloride can be associated with emergence phenomena. Typically, opioid induced respiratory depression is treated with Naloxone, while ketamine associated emergence is treated with benzodiazepines.

If required, rescue analgesia (first line entonox or IV paracetamol, 2nd line further titrated open label morphine) will be available and captured as a trial outcome.

Design and theoretical/conceptual framework:

This will be a pragmatic phase 3, two large NHS ambulance trusts, blinded, individually randomised, controlled clinical and cost-effectiveness trial, with an internal pilot.

Protection against bias:

All patients, attended by a trial paramedic, reporting severe pain following trauma will be eligible for inclusion in the study. To limit selection bias treatment allocation will be concealed using pre-randomised drug packs. The trial drugs, morphine and ketamine, each have distinct side effect profiles. The occurrence of drug side effects, such as nystagmus or hypotension, has the potential to impact blinding. To minimise detection and performance bias we will use clinical protocols to guide treatments. In accordance with Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines we advocate slow titration to effect, with administration of drug stopping once the patient reports adequate pain relief. This approach limits the amount of drug administered and reduces the likelihood of side effects associated with bolus drug administration. To reduce attrition bias we will seek informed, written consent as soon as the initial emergency has passed. This will help minimise loss to follow-up. Data required for our primary outcome and many of our secondary outcomes will be collected before arrival at hospital. Our approach to follow-up is designed to minimise participant inconvenience. In this way we hope to maximise the available data to determine chronic pain, economic and quality of life outcomes. To guard against reporting bias the trial will be registered with ISCRTN, and the trial protocol with statistical analysis plan will be published *a-priori*.

Sampling:

Sample size calculation:

The International Association for the Study of Pain have quantified clinically meaningful improvements in pain intensity.[77] 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.[77]

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 Percent 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.[78] 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.

We calculate a sample of 446 subjects is required, recruiting 223 to each arm of the study to detect a 1 point difference (0 – 10 NRS), in effectiveness between morphine and ketamine. This estimation assumes 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%."

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Recruitment and retention:

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).

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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 trial paramedics should be trained by month 10, when monthly recruitment will plateau at 40 patients per month (see figure 2).

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.

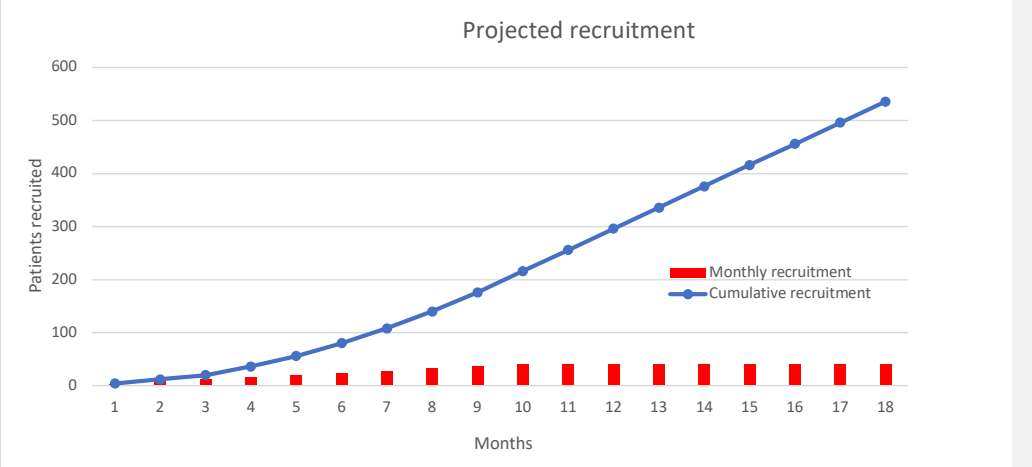

Figure 2 – Projected recruitment

Target population:

Adult patients (age ≥16 years) with severe pain following trauma, judged by the paramedic as requiring treatment with IV morphine or equivalent.

Inclusion criteria:

- Age >16
- Patient reports severe pain due to an acute traumatic injury
- Vascular access obtained

Exclusion criteria:

- Known or suspected pregnancy[1]
- Unable to articulate severity of pain using the 0-10 numerical rating scale
- Ketamine or opioid analgesia received prior to screening
- Contraindication to either ketamine or morphine[2]
- Patient declines participation

[1] Although pregnancy is not a contra-indication to Ketamine 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. We recognize that a potentially eligible patient may not suspect that they are pregnant. In this scenario the trial 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.

[2] Exclusions to morphine / ketamine will be drawn from ambulance guidelines, BNF and summary of medical product characteristics. Paramedics will be trained to recognize these exclusions and an aid memoir will be included with trial materials.

In order to meet the CONSORT guidelines for design and reporting of RCTs, we will collect data on all patients that present with severe pain. Reasons for ineligibility, refusal to consent and protocol violations will be documented and reported as a part of the CONSORT flow diagram.

Setting:

- West Midlands Ambulance Service University NHS Foundation Trust.
- Yorkshire Ambulance Service NHS Trust.

Data collection:

A data dictionary and bespoke case report form will ensure consistent data are captured through the trial.

- Baseline characteristics (patient demographics, vital signs) will be captured from the ambulance service electronic patient record.
- Primary outcome data will be calculated using pain intensity scores collected from the ambulance service electronic patient record.
- Secondary outcome data will be collected from the ambulance service electronic patient record and telephone administered Brief Pain Inventory – Short Form (BPI-SF)[73] at 3 months post injury.
- Resource use and preference-based health-related quality of life outcomes will be collected at 3 and 6 months post injury using variants of the Client Service Receipt Inventory and a validated multi-attribute utility measure (EQ-5D-5L).

Data analysis:

Primary analysis:

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.

Secondary analyses:

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 proporational hazard method.

Interim analyses:

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.

Sub-group analyses:

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 (injury severity score ≤15 or > 15)
- Gender (male, female)
- Alternative parenteral analgesia prior to randomization (yes, no)

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.[79] 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 and ambulance vehicles in attendance, duration of emergency response and cummulative 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 or around hospital discharge, and 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.[80] 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.

6 DISSEMINATION, OUTPUTS AND ANTICIPATED IMPACT

What do you intend to produce from your research?

This study will produce the following outputs:
1) Education and training materials
2) Conference presentations at UK, European and international ambulance and prehospital care meetings
3) Publications in peer reviewed journals
4) Lay summary, including infographic, of research findings.

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How will you inform and engage patients, NHS and the wider population about your work?

Our dissemination strategy will aim to increase awareness of our findings, stimulate improvements in prehospital pain management, provide an evidence base for future research funding and promote public engagement and understanding of the research. It will target policy makers and commissioners; Regional Trauma Networks; Ambulance services; Health care providers; Academic audiences; Patients and the public; and Trauma and pain charities and advocacy groups.

Our patient and public co-applicant will be integrally involved in developing and implementing the dissemination plan. His focus on improving care for victims of trauma gives him an insight which complements the experiences of clinical and academic co-applicants. We have strong links with guideline development groups and our previous research has influenced a number of national and international guidelines. We will also harness the contacts and professional networks of collaborators which contain key opinion leaders in prehospital care. This will ensure results are shared across all regional and national networks and to the highest policy making levels, to facilitate adoption of the research findings.

How will your outputs enter our health and care system or society as a whole?

We will distribute our findings to stakeholders with an interest in pain management. Our research will inform further development of an evidence-based pain management guideline for paramedics employed by NHS ambulance services.

What further funding or support will be required if this research is successful?

Our work may identify the need for further research, which will be summarized and presented to NIHR and may inform future grant applications. The introduction of new drugs to paramedics will likely incur training costs for the NHS ambulance services but this would be met through existing systems.

What are the possible barriers for further research, adoption and implementation?

The national co-ordination of ambulance services and use of national clinical practice guidelines managed through the Association of Ambulance Chief Executives and Joint Royal College Ambulance Liaison Committee minimizes barriers to further research, development, adoption and implementation. Our coapplicant Alison Walker is a member of the National Ambulance Medical Directors group and will lead on national implementation of the research findings in to practice using the NICE guidance on reducing barriers to implementing research in to practice. Patient group directives, written in accordance with NICE guidelines and compliant with the Schedule 16 of the Human Medicines Regulations 2012 will be developed to support implementation. Ketamine is no longer under patent and is available from several manufacturers in the UK.

What do you think the impact of your research will be and for whom?

Our research will support an evidence-based approach to prehospital pain management for paramedics employed by NHS ambulance services. It will improve healthcare quality for patients experiencing severe pain following trauma and their families 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.

7 PROJECT / RESEARCH TIMETABLE

Core funding within Warwick CTU will enable us to initiate pre-contract work to ensure a timely start to the project. Clinical trial staff will be assigned from our pool of expert trial managers. The main trial will be preceded by an internal pilot study which is described above. On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial. We will continue monitoring processes to ensure the trial is delivered as planned. We have budgeted for 2 Trial Steering Committee and 2 Data Monitoring Committee meetings each year to include: initiation, post pilot study and with the others to be confirmed and planned following the results of the internal pilot phase.

Month	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36
Oversight												
TMG	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
PPI	x	x	x	x	x	x	x	x	x	x	x	x
TSC/DMEC	x		x		x		x		x			x
Trial												
Set up & approvals												
Training												
Pilot (n)			20	60								
Main trial (n)					96	120	120	120				
Recruitment (n)			20	80	176	296	416	536				
Follow-up												
Analysis												
HTA Report												

8 PROJECT MANAGEMENT

Sponsor and contracting NHS organisation:

The legal sponsor for the trial and contracting organisation will be the University of Warwick. Sub-contracts will be established with NHS partner organisation in accordance with NIHR terms.

Administration:

The study will be coordinated by the UKCRC registered Warwick CTU which has specific expertise in undertaking studies in emergency and critical care. The study will be conducted according to the defined SOPs. The CTU will be responsible for protocol development, ethical and governance approvals, database development and data management, randomisation, trial management and monitoring, analysis of the data and reporting.

Trial management group (TMG):

A Trial Management Group (TMG) chaired by the Chief Investigator (Smyth), supervised by the Co-Chief Investigator (Perkins) and attended by CTU staff, and co applicants will oversee the management of the trial. The TMG will meet face to face and/or by teleconference on a monthly basis. A GANNT diagram will be produced indicating key progress targets / milestones and reviewed at each meeting. Site by site recruitment will be reported to the TMG monthly using the UKCRC endorsed monitoring tool. A dynamic risk assessment will be maintained and reviewed monthly. All the day-to-day activity will be managed by Warwick CTU's full time Clinical Trial Manager working under the direction of the Chief Investigator (Smyth,) who in turn will be supervised by the Co-Chief Investigator (Perkins, Director CTU). This ensures that there is a single point of contact for all enquiries and a single dissemination point for project communications.

Training:

In collaboration with participating Ambulance Trusts, Warwick CTU will develop educational and training material for participating paramedics. These training materials will help standardise recruitment processes,

trial treatments and patient care, and ensure accurate, complete and reliable data are collected. Training will include online learning materials which will remain accessible to participating paramedics throughout the trial, and face-to face instruction. Delivery of face-to-face instruction to participating paramedics at collaborating sites will be the responsibility of each participating Ambulance Trust. 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 protocol and training manual. Training materials including slide shows, videos, FAQs and written material will be available.

Trial steering committee (TSC):

The TSC will provide oversight with respect to the conduct of the study. An independent chair will lead the TSC with at least two other independent members. It will incorporate at least one patient/public representative as well as both co-chief investigators. The TSC roles are outlined in the HTA research governance guidelines as follows: agree proposals for substantial protocol amendments; maintain the rights, safety and wellbeing of participants in the trial; monitor and supervise progress; consider new information relevant to the trial; consider recommendations from DMEC; inform and advise on all aspects of the trial.

Data monitoring and ethics committee (DMEC):

This will comprise 2 independent clinicians with experience in clinical trials and an independent statistician. One of the independent clinicians will have experience in undertaking clinical trials in emergency or acute care. The DMEC charter will be based on the DAMOCLES study group template.[81] Its roles will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies.

9 ETHICS

The study will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki and those in Good Clinical Practice. We will apply separately for ethical approval to a research ethics committee identified for CTIMP trials involving patients without capacity. The ethics application made by the Co-Chief Investigator (Smyth), once approved, will cover all collaborating sites. The trial protocol will be prepared in compliance with the SPIRIT 2013 guidelines.[82] The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register. The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institutions for written approval.

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. We outline our proposed approach to this challenge in the consent section above. 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.[83]

10 PATIENT AND PUBLIC INVOLVEMENT

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 (2 members). We will recruit one young person and one female as additional collaborators in our study to ensure all patient groups are adequately represented

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 (monthly initially and then 3 monthly) 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.

11 PROJECT / RESEARCH EXPERTISE

The trial will be coordinated by Warwick CTU, which has considerable experience conducting randomized controlled trials in prehospital, emergency and critical care settings. This proposal draws together an experienced team of health service researchers with a strong track record in emergency care research. Our team comprises clinician scientists (Smyth (CI), Perkins (Co-CI), Yeung, Fuller), methodologists (Lall (statistics), Petrou and Achana (health economics)) and experienced PPI (Buckley). Smyth, a paramedic and former NIHR Clinical Doctoral Research Fellow will lead the project under the guidance and direct supervision of Perkins (NIHR Senior Investigator and Director Warwick CTU). The trial will be supported by a trained trial manager, trial coordinator, junior statistician and junior health economist, quality assurance manager and a trial assistant.

12 SUCCESS CRITERIA AND BARRIERS TO PROPOSED WORK

A full risk assessment will be undertaken prior to commencement of the trial and reviewed regularly throughout the conduct of the trial. This will enable a dynamic and on-going assessment and management of risks through the trial.

An outline of the key success criteria, barriers and mitigation is presented below.

Success criteria	***Barrier***	***Mitigation***
Ethics and regulatory approval	Difficulty obtaining ethics approval due to lack of capacity among research subjects	Experienced team with track record of designing and delivering research in accordance with the EU / UK Clinical Trials Regulations and ethical standards
Recruitment to time and target	Insufficient infrastructure	Experienced sites with track record of recruiting to trials in prehospital care.
		CRN support

	Recruitment slower than expected	Active site management by WCTU to monitor recruitment and intervene early in event of slower than anticipated recruitment
		Monthly site teleconferences
		Systematic approach to explore barriers to recruitment
	Clinicians do not follow protocol	Co-develop protocol with clinical teams.
		Monitoring and early feedback for non-compliance
		Withdrawal of sites with sustained non-compliance
Complete patient follow-up	Questionnaires not completed	Established system for patient follow-up (letter, phone call, GP contact, support groups)
		Monthly monitoring of return rates by TMG.
		Reporting to TSC meetings

A randomised controlled trial of **P**aramedic **A**nalgesia **C**omparing **K**etamine and **M**orphi**N**e in trauma (PACKMaN)

Months 0-6 set up

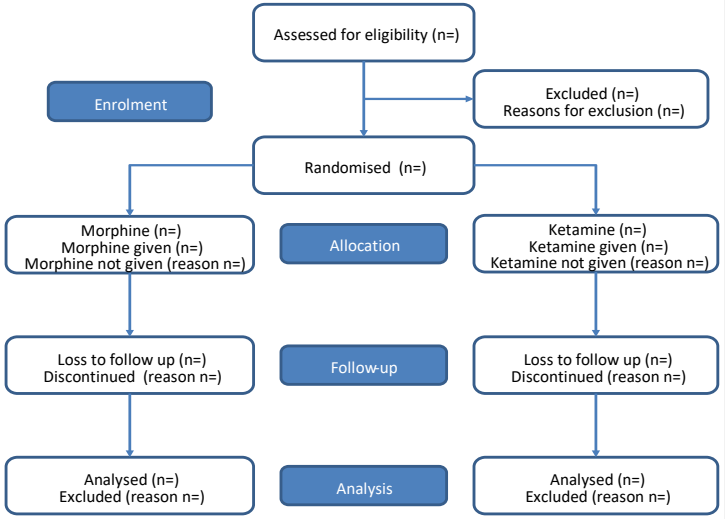
Months 7-15 training

Months 7-12 pilot phase

Months 13-24 main trial

Months 10-30 follow-up

Months 31-36 reporting



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Project reference: NIHR128086

1 FULL TITLE OF PROJECT

Prehospital analgesia comparing ketamine and morphine in trauma. A randomised controlled trial and economic evaluation

2 SUMMARY OF RESEARCH

Research question: Is ketamine superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics?

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

Aims and objectives:

Aim: To deliver a pragmatic, blinded, individually randomised, controlled trial, in two NHS Ambulance Trusts (informed by an internal pilot), which will determine the clinical and cost effectiveness of ketamine and morphine, among adult patients, with severe pain following trauma and who are attended by paramedics.

Primary objective: To determine whether paramedic administered ketamine or morphine provides more effective pain relief for patients reporting severe pain following trauma.

Secondary objectives: 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.

Design: Pragmatic, individually randomised, controlled, blinded, trial, with economic evaluation.

Setting:

- West Midlands Ambulance Service University NHS Foundation Trust which serves a population of 5.2 million over 5 counties and 7 cities.
- Yorkshire Ambulance Service NHS Trust which serves a population of 8.6 million

Population: Adult patients (age ≥16 years) with severe pain following trauma, judged by the paramedic as requiring treatment with IV morphine or equivalent.

Inclusion criteria:

1. Age >16
2. Patient reports severe pain due to an acute traumatic injury
3. Vascular access obtained

Exclusion criteria:

1. Known or suspected pregnancy
2. Unable to articulate severity of pain using the 0-10 numerical rating scale
3. Ketamine or opioid analgesia received prior to screening
4. Contraindication to either ketamine or morphine
5. Patient declines participation

Randomisation: Specially prepared, sequentially numbered treatment packs containing ampoules of either morphine or ketamine which are identical in appearance. Allocation will be concealed from study personnel, ambulance staff and patients.

Intervention: Ketamine hydrochloride.

Project reference: NIHR128086

Comparator: Morphine sulphate.

Primary outcome:

Sum of Pain Intensity Difference (SPID) score. The SPID is a patient focused measurement which combines the magnitude and duration of pain relief.

Secondary outcomes:

Effectiveness of pain relieve /overall patient experience
Side effects and adverse events
Resource use
Longer term outcomes
Cost effectiveness

Sample size: Using 1:1 randomisation, a power of 90%, significance level of 5% and a withdrawal/nonresponse rate of 15%, we require 446 subjects to detect a clinically relevant reduction of 1-point different (standard deviation=3.0) points on a 0-10 numeric pain scale.

Timeline:
Month 0-8: study protocol, regulatory approvals, IMP manufacture
Month 9-18: paramedic training
Month 9-14: internal pilot phase
Month 15-24: main trial recruitment
Month 12-30: follow-up
Month 31-36: analysis and reporting

Anticipated impact and dissemination: 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.

3 BACKGROUND AND RATIONALE

At least 70% of Ambulance calls are related to patients experiencing pain.[1] Observational studies provide evidence that current treatments leave many patients with in-adequate 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. The World Health Organisation declared in 2004 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

posttraumatic 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 approaches

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

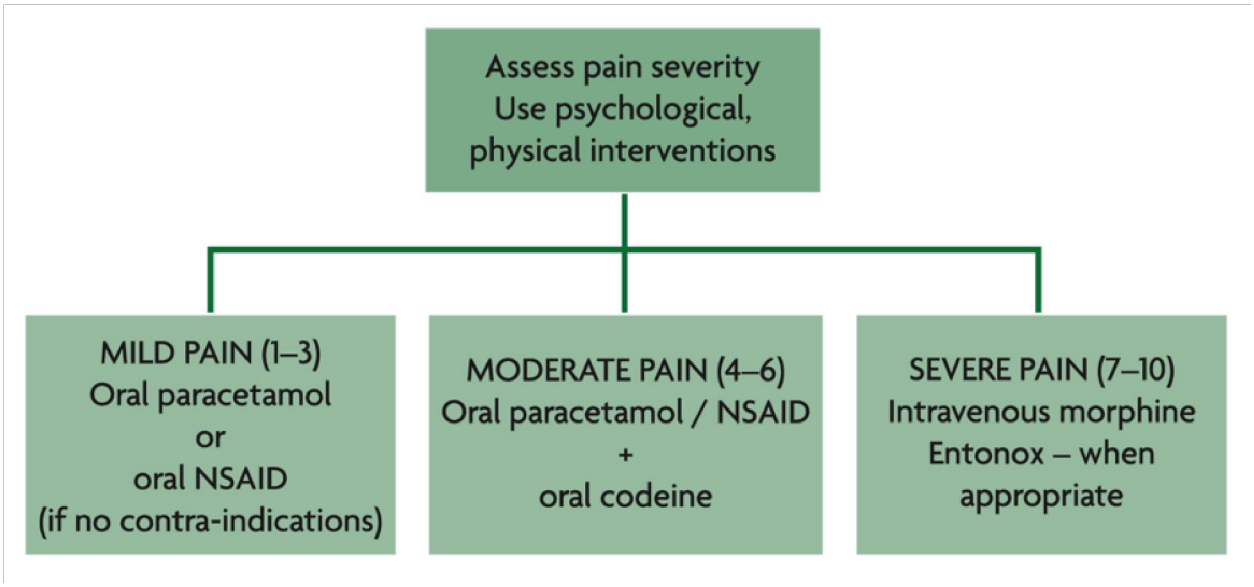


Figure 1 Approach to prehospital pain management

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 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. Seriouas adverse outcomes have not been reported even though overdoses of 5 to 100 times the intended dose have been inadvertently administered.[27] Due to it's 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.

Current practice

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. Assessment of the certainty of evidence using the GRADE recommendations, the 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 randomized 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 totaling 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 2 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 generalizability 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 clinicians willingness to enroll 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.

3a WHY IS THIS RESEARCH NEEDED NOW?

i. *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.

ii. *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.

iii. *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.

iv. *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.

v. *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.

vi. *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]

4 AIMS AND OBJECTIVES

Overall aim:

To deliver a pragmatic, blinded, individually randomised, controlled trial, in two NHS Ambulance Trusts, informed by an internal pilot), which will determine the clinical and cost effectiveness of ketamine and morphine, among adult patients, with severe pain following trauma and who are attended by paramedics.

Primary Objective:

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, 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.

Secondary objectives:

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.

Specifically we will assess:

1. Effectiveness of pain relief overall patient experience from randomisation to arrival at hospital
   a. Total Pain Relief (TOTPAR) score (using a 0-10 numerical rating scale)
   b. Time to effective analgesia, duration of analgesia
   c. Requirement for rescue analgesia
   d. Proportion of patients with a pain intensity score below 4/10 (0-10 numerical rating scale) on arrival at hospital
   e. Patient Global Impression of Change on arrival at hospital
2. Incidence of side effects and adverse events
   a. Airway: vomiting, aspiration, advanced airway management
   b. Respiratory: desaturation, need for ventilatory support
   c. Cardiovascular: arrhythmia, hypotension and hypertension
   d. Neurologic: sedation, excitatory movements, adverse behavioural reactions
   e. Other: allergic reaction, serious unexpected serious adverse reactions
3. Resource use
   a. Ambulance job cycle time (scene arrival to arrival at hospital)
   b. CT scan use
   c. Hospital or ICU admission
   d. Length of stay ED, ICU, Hospital
4. Longer term outcomes
   a. Chronic pain using BPI-SF at 3 months from randomisation
   b. Health-related quality of life at 3 and 6 months from randomisation EQ-5D-5L
5. Cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained using EQ-5D 5L (at hospital discharge, 3 and 6 months)

5 RESEARCH PLAN / METHODS

Trial design:

Our study is designed to address the research gap identified by the NICE Major Trauma Guideline (NG39). Specifically, *"Is morphine clinically and cost effective compared with ketamine for first-line pharmacological pain management (in both pre-hospital and hospital settings) in patients with major trauma?"* This study is a pragmatic, double blind, randomised controlled trial and economic evaluation, with an internal pilot and blinded assessment of outcomes up to 6 months after randomisation. In PICO terms:

Population:	Adult patients reporting severe pain following acute traumatic injury, who are able to express a pain intensity score utilising a 0-10 numeric rating scale (NRS).
Intervention:	Intravenous ketamine hydrochloride
Comparator:	Intravenous morphine sulphate
Outcomes:	Clinical and cost-effectiveness outcomes up to 6 months

Research question:

Is ketamine superior to morphine for the management of acute severe pain from traumatic injury treated by NHS paramedics?

Study:

Internal pilot study:

The main study will be preceded by a six month internal pilot. The progression of the pilot is informed by recently published best practice guidelines.[65] We anticipate that by six months we will recruit a minimum of 48 patients (24 per treatment arm, 9% of the total sample).[65] The pilot will take place in two ambulance hubs, one from each participating ambulance service. The pilot will be used to confirm training, recruitment, compliance, data capture and follow-up assessments.

Our recruitment rate is anticipated to be 4 patients, per 50 participating ambulance paramedics, per month open to recruitment. Success criteria for recruitment will be based on the traffic light system:

Go:	75-100% recruitment: progress to main trial following a review of screening logs and protocol. Any barriers for recruitment will be addressed
Amend:	50-75% recruitment: progress to main trial with additional sites being recruited as well as a screening log and protocol review
Stop:	less than 50% recruitment: the decision to progress will be made by the Trial Steering Committee in association with the HTA secretariat. Protocol compliance and the completeness of follow-up data will be reviewed by the DMC and TSC, noting that six months follow-up data will not be completed at the end of the pilot

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 deviations, violations, 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.

Main study:

The remaining sample of 446 patients (223 per treatment arm) will be enrolled into the main study. The main study will take place in two English ambulance services which have a proven track record of successful participation in clinical trials. The main study will recruit over a period of 12 months.

We will undertake a process evaluation and assess the implementation of trial procedures e.g. training, auditing screening logs, recruitment, reasons for exclusion and protocol compliance. Any indication of poor compliance will trigger additional training for participating paramedics. We will hold monthly teleconference meetings with the participating ambulance trusts to identify any recruitment issues and any difficulty with implementing the trial protocol.

We will provide feedback periodically to participating ambulance trusts based on performance monitoring described above and, if required, refine educational packages to target any specific barriers to recruitment.

Consent

We have carefully considered the approach to consent in the context of advice from our patient / public representatives, a review of the HRA guidance in relation to Clinical Trials of Investigational Medicinal Products (CTIMPS) in an emergency setting. We have applied our teams and other research teams previous experience of research in this setting. As we develop the full trial protocol, we will have further opportunities for input from our patient and public collaborators.

The clinical trials regulations require that for consent to be considered legal, it must be provided in writing, the patient must have capacity, it must be given voluntarily without undue influence, and given by someone who has been adequately informed and a fair choice.

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 due to the nature of their injuries (e.g. broken arm) or location (e.g. trapped in the wreckage of a car). Withholding pain relief to obtain written informed consent has in some settings been considered coercion and is not regarded as best practice. It is our assessment that few patients with acute, severe traumatic pain will have sufficient physical and mental capacity to provide written informed consent.

The urgency with which treatment for acute severe pain must be provided precludes it being practical to obtain written informed consent from a personal legal representative as to do so would delay treating the patients pain. The enrolling paramedic will not have timely access to a professional legal representative making such an approach impractical.

We will therefore seek approval from the Research Ethics Committee to enrol patients in to the clinical trial using the provisions within the Clinical Trials Regulations (2006, No 2984) for adult patients who lack capacity on the basis that:

- The patient is incapacitated
- Treatment needs to be given urgently
- It is necessary to take urgent action to administer the drug for the purposes of the trial
- It is not reasonably practicable to obtain consent from a legal representative
- The procedure is approved by a NHS Research Ethics Committee
- Consent is sought from a legal representative as soon as possible

Consent process:

Prior to enrolment, the paramedic will provide brief verbal information to the patient (and / or personal legal representative) about the intention to enrol the patient in the trial and confirm their willingness in principle to participate. If the patient or personal legal representative indicate any objection, standard care will be provided without prejudice.

Once the initial emergency has passed, and the patients pain is under control, the enrolling paramedic will assess the patients capacity to determine if they are able to make an informed decision to continue in the trial. The paramedic will seek consent to continue participation in the trial as follows:

Patient has capacity to consent - Where the paramedic assesses that the patient has capacity, then they will provide written information (participant information sheet) regarding the study and seek written, informed consent from the patient to continue in the trial.

Patient lacks capacity to consent - Where the paramedic assesses the patient lacks capacity, then they will seek consent from a personal legal representative provided this will not unduly delay the provision of continuing clinical care. 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. Research staff will continue with attempts to obtain written informed consent from the participant at each point of contact.

Patient or legal representative withdraws consent - If at any point following enrolment the patient (or their legal representative) indicates that they no longer wish to participate in the trial then no further study related treatment will be provided, and usual care will provided. All non-identifiable data up to the point of withdrawal will be retained in accordance with the trials regulations. No further data collection will be conducted from this point onwards.

This approach is consistent with the EU Clinical Trials Directive[69] and the soon to be implemented EU Clinical Trials Regulations.[70] We will additionally collaborate with our Ambulance Trust partners and PPI collaborators to robustly monitor the consent process during the pilot phase to ensure all our obligations to patients are met, and that the consent process is acceptable to participants. We will confirm these consent arrangements with an independent NHS Research Ethics Committee (REC) prior to commencement of the trial.

Randomisation and blinding:

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 study statistician. 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.

Outcome measures and justification:

Outcome measures have been selected to address the commissioning brief, namely to evaluate a potentially sustainable intervention to improve the management of acute pain in the pre-hospital setting.

Outcome	**Trial outcome**	**Rationale**
Primary outcome	Sum of Pain Intensity Difference	Recommended by IMMPACT and EMA

Secondary outcomes	Total Pain Relief (TOTPAR)	Recommended by IMMPACT and EMA
	Time to effective analgesia and duration of analgesia	Recommended by IMMPACT and EMA
	Proportion of patients requiring rescue analgesia during prehospital care	Advocated by IMMPACT recommendations
	Proportion of patients with a pain <4/10 on arrival at hospital	Advocated by IMMPACT recommendations
	Patient Global Impression of Change	Recommended by IMMPACT and EMA
	Incidence of adverse events and serious adverse events	Advocated by IMMPACT recommendations
	Resource use	To quantify the impact on the emergency care pathway
	Long term outcomes – HRQL and chronic pain	Recommended by IMMPACT and EMA and referred to in the commissioning brief
Cost effectiveness	Cost-effectiveness from the perspective of NHS and personal social services	Need identified by NICE (NG39)

IMMPACT - Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations.[63]
EMA – European Medicines Agency.[64]

Primary outcome:

As advocated by IMMPACT core outcome recommendations, our primary outcome is the Sum of Pain Intensity Difference (SPID). The SPID is a patient focused measurement which combines the magnitude and duration of relief in a single score.

Sum of Pain Intensity Difference is calculated using the pain-intensity difference (PID). The PID is the difference between current pain intensity (0-10 NRS) and baseline pain intensity (0-10 NRS). Baseline pain intensity is the pain intensity (0-10 NRS), before analgesia is administered. Pain intensity will be measured at 10 minute intervals from randomisation to arrival at hospital. SPID is the summation of the PID at each interval, weighted according to the amount of time since the previous PID assessment; it approximates the area under the curve for PID over time. The benefit of using SPID is that it takes into account individual differences in baseline pain intensity, improvements in pain intensity and time. SPID is also reported as a percentage of maximum possible SPID (%SPID). Maximum possible SPID is the value that would be achieved if the patient were pain free (NRS = 0) for the entire study period.

We have selected the 0-10 numerical rating scale in preference to other pain intensity scales as it is easily understood by participants, is easily translatable[63] and is currently used by NHS Ambulance Services.

Secondary outcomes:

As advocated by IMMPACT and EMA and our patient and public partner, our secondary outcomes will include:

1. Overall effectiveness of pain relief / patient experience from randomisation to hospital admission

   a) Total Pain Relief (TOTPAR), a summary measure that integrates serial assessments of a pain intensity over time (the prehospital interval). It is a time-weighted measure of total area under the pain relief curve.
   b) Time to effective analgesia, duration of analgesia.

c) Proportion of patients requiring rescue analgesia during prehospital care.
d) Proportion of patients with a pain intensive score below 4/10 on NRS on arrival at hospital
e) Patient Global Impression of Change at hospital. Patient focused outcome which assesses improvement and overall satisfaction with treatment—assessed by the seven-point Patient Global Impression of Change scale.[71]

2. Side effects and adverse events

a) Airway: vomiting, aspiration, advanced airway management
b) Respiratory: desaturation, need for ventilatory support
c) Cardiovascular: arrhythmia, hypotension and hypertension
d) Neurologic: sedation, excitatory movements, adverse behavioural reactions
e) Other: allergic reaction, serious unexpected serious adverse reactions

3. Resource use
a) Ambulance job cycle time (scene arrival to arrival at hospital)
b) CT scan use
c) Hospital or intensive care admission
d) Length of stay in emergency department, intensive care, hospital

4. Longer term outcomes
a) Chronic pain using BPI-SF at 3 months (see below)
b) Health-related quality of life at 3 months and 6 months using EQ-5D-5L

5. Cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained using EQ-5D 5L (at hospital discharge, 3 and 6 months)

We will assess chronic pain at 3 months post recruitment.[72] We will follow-up via telephone and use the Brief Pain Inventory – Short Form (BPI-SF).[73] The BPI-SF is an 11-item, pain-specific quality of life measure. It is split into two parts: a four item 'pain severity' domain and a seven-item 'pain interference' scale. It is reported as a total pain severity scale, though for the purposes of chronic pain, pain average is felt to be the most accurate representation of a person's pain.[73] The BPI-SF has been validated in chronic non-cancer patients and captures pertinent information including pain intensity, pain medications and patient reported interference on mood, sleep and physical function.[74] [75] It can be successfully completed via telephone.[76]

Health technology being assessed:

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.

Control: **morphine sulphate** *(10mg in 10ml)*
- Initial dose: 10ml (10mg) titrated to effect (2ml per minute for 5 minutes)
- Repeat dose: 2ml (2mg) (minimum of 5 minutes elapsed since last dose)
- Maximum cumulative dose: 20 ml (20mg)

Intervention: **ketamine hydrochloride** *(15mg in 10 ml)*
- Initial dose: 10ml (15mg) titrated to effect (2ml per minute for 5 minutes)
- Repeat dose: 2ml (3mg) (minimum of 5 minutes elapsed since last dose)
- Maximum cumulative dose: 20 ml (30mg)

If the patient weighs less that 50kg (actual or estimated), or if the paramedic providing treatment has concerns regarding patient frailty, then treatment should be adjusted. In such circumstances the paramedic will titrate the trial drug administering 1ml per minute over 10 minutes, rather than 2ml per minute over 5 minutes.

Slowing the rate at which the trial drug is administered will reduce the likelihood of a frail patient inadvertently receiving more drug than clinically required and lower the risk of adverse effects in this population.

Both morphine and ketamine have predictable side effects that may require subsequent treatment. Although rare (<5%), morphine sulphate may cause respiratory depression and ketamine hydrochloride can be associated with emergence phenomena. Typically, opioid induced respiratory depression is treated with Naloxone, while ketamine associated emergence is treated with benzodiazepines.

If required, rescue analgesia (first line entonox or IV paracetamol, 2nd line further titrated open label morphine) will be available and captured as a trial outcome.

Design and theoretical/conceptual framework:

This will be a pragmatic phase 3, two large NHS ambulance trusts, blinded, individually randomised, controlled clinical and cost-effectiveness trial, with an internal pilot.

Protection against bias:

All patients, attended by a trial paramedic, reporting severe pain following trauma will be eligible for inclusion in the study. To limit selection bias treatment allocation will be concealed using pre-randomised drug packs. The trial drugs, morphine and ketamine, each have distinct side effect profiles. The occurrence of drug side effects, such as nystagmus or hypotension, has the potential to impact blinding. To minimise detection and performance bias we will use clinical protocols to guide treatments. In accordance with Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines we advocate slow titration to effect, with administration of drug stopping once the patient reports adequate pain relief. This approach limits the amount of drug administered and reduces the likelihood of side effects associated with bolus drug administration. To reduce attrition bias we will seek informed, written consent as soon as the initial emergency has passed. This will help minimise loss to follow-up. Data required for our primary outcome and many of our secondary outcomes will be collected before arrival at hospital. Our approach to follow-up is designed to minimise participant inconvenience. In this way we hope to maximise the available data to determine chronic pain, economic and quality of life outcomes. To guard against reporting bias the trial will be registered with ISCRTN, and the trial protocol with statistical analysis plan will be published *a-priori*.

Sampling:

Sample size calculation:

The International Association for the Study of Pain have quantified clinically meaningful improvements in pain intensity.[77] 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.[77]

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 Percent 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.[78] 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.

We calculate a sample of 446 subjects is required, recruiting 223 to each arm of the study to detect a 1 point difference (0 – 10 NRS), in effectiveness between morphine and ketamine. This estimation assumes 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%."

Recruitment and retention:

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 trial paramedics should be trained by month 10, when monthly recruitment will plateau at 40 patients per month (see figure 2).

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.

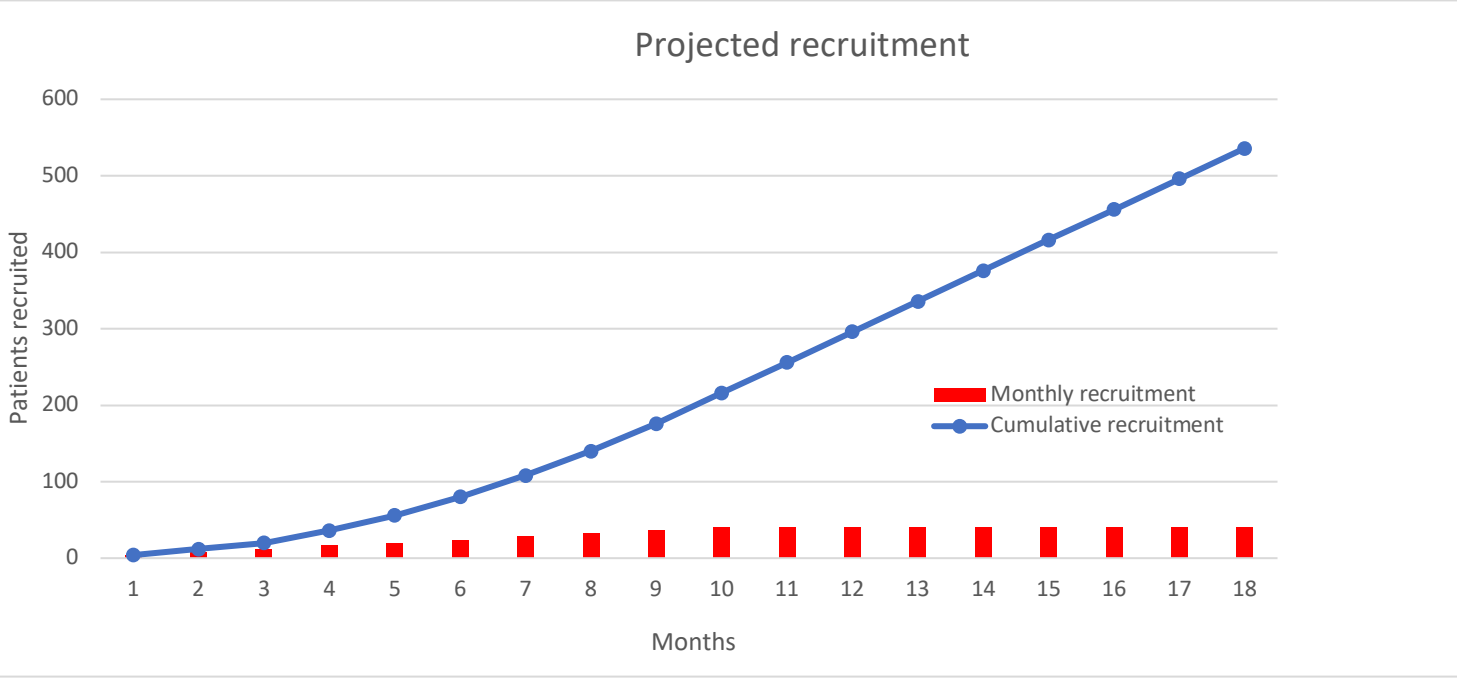


Figure 2 – Projected recruitment

Target population:

Adult patients (age ≥16 years) with severe pain following trauma, judged by the paramedic as requiring treatment with IV morphine or equivalent.

Inclusion criteria:

- Age >16
- Patient reports severe pain due to an acute traumatic injury
- Vascular access obtained

Exclusion criteria:

- Known or suspected pregnancy[1]
- Unable to articulate severity of pain using the 0-10 numerical rating scale
- Ketamine or opioid analgesia received prior to screening
- Contraindication to either ketamine or morphine[2]
- Patient declines participation

[1] Although pregnancy is not a contra-indication to Ketamine 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. We recognize that a potentially eligible patient may not suspect that they are pregnant. In this scenario the trial 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.

[2] Exclusions to morphine / ketamine will be drawn from ambulance guidelines, BNF and summary of medical product characteristics. Paramedics will be trained to recognize these exclusions and an aid memoir will be included with trial materials.

In order to meet the CONSORT guidelines for design and reporting of RCTs, we will collect data on all patients that present with severe pain. Reasons for ineligibility, refusal to consent and protocol violations will be documented and reported as a part of the CONSORT flow diagram.

Setting:

- West Midlands Ambulance Service University NHS Foundation Trust.
- Yorkshire Ambulance Service NHS Trust.

Data collection:

A data dictionary and bespoke case report form will ensure consistent data are captured through the trial.

- Baseline characteristics (patient demographics, vital signs) will be captured from the ambulance service electronic patient record.
- Primary outcome data will be calculated using pain intensity scores collected from the ambulance service electronic patient record.
- Secondary outcome data will be collected from the ambulance service electronic patient record and telephone administered Brief Pain Inventory – Short Form (BPI-SF)[73] at 3 months post injury.
- Resource use and preference-based health-related quality of life outcomes will be collected at 3 and 6 months post injury using variants of the Client Service Receipt Inventory and a validated multi-attribute utility measure (EQ-5D-5L).

Data analysis:

Primary analysis:

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.

Secondary analyses:

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 proporational hazard method.

Interim analyses:

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.

Sub-group analyses:

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 (injury severity score ≤15 or > 15)
- Gender (male, female)
- Alternative parenteral analgesia prior to randomization (yes, no)

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.[79] 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 and ambulance vehicles in attendance, duration of emergency response and cummulative 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 or around hospital discharge, and 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.[80] 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.

6 DISSEMINATION, OUTPUTS AND ANTICIPATED IMPACT

What do you intend to produce from your research?

This study will produce the following outputs:
1) Education and training materials
2) Conference presentations at UK, European and international ambulance and prehospital care meetings
3) Publications in peer reviewed journals
4) Lay summary, including infographic, of research findings.

How will you inform and engage patients, NHS and the wider population about your work?

Our dissemination strategy will aim to increase awareness of our findings, stimulate improvements in prehospital pain management, provide an evidence base for future research funding and promote public engagement and understanding of the research. It will target policy makers and commissioners; Regional Trauma Networks; Ambulance services; Health care providers; Academic audiences; Patients and the public; and Trauma and pain charities and advocacy groups.

Our patient and public co-applicant will be integrally involved in developing and implementing the dissemination plan. His focus on improving care for victims of trauma gives him an insight which complements the experiences of clinical and academic co-applicants. We have strong links with guideline development groups and our previous research has influenced a number of national and international guidelines. We will also harness the contacts and professional networks of collaborators which contain key opinion leaders in prehospital care. This will ensure results are shared across all regional and national networks and to the highest policy making levels, to facilitate adoption of the research findings.

How will your outputs enter our health and care system or society as a whole?

We will distribute our findings to stakeholders with an interest in pain management. Our research will inform further development of an evidence-based pain management guideline for paramedics employed by NHS ambulance services.

What further funding or support will be required if this research is successful?

Our work may identify the need for further research, which will be summarized and presented to NIHR and may inform future grant applications. The introduction of new drugs to paramedics will likely incur training costs for the NHS ambulance services but this would be met through existing systems.

What are the possible barriers for further research, adoption and implementation?

The national co-ordination of ambulance services and use of national clinical practice guidelines managed through the Association of Ambulance Chief Executives and Joint Royal College Ambulance Liaison Committee minimizes barriers to further research, development, adoption and implementation. Our coapplicant Alison Walker is a member of the National Ambulance Medical Directors group and will lead on national implementation of the research findings in to practice using the NICE guidance on reducing barriers to implementing research in to practice. Patient group directives, written in accordance with NICE guidelines and compliant with the Schedule 16 of the Human Medicines Regulations 2012 will be developed to support implementation. Ketamine is no longer under patent and is available from several manufacturers in the UK.

What do you think the impact of your research will be and for whom?

Our research will support an evidence-based approach to prehospital pain management for paramedics employed by NHS ambulance services. It will improve healthcare quality for patients experiencing severe pain following trauma and their families 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.

7 PROJECT / RESEARCH TIMETABLE

Core funding within Warwick CTU will enable us to initiate pre-contract work to ensure a timely start to the project. Clinical trial staff will be assigned from our pool of expert trial managers. The main trial will be preceded by an internal pilot study which is described above. On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial. We will continue monitoring processes to ensure the trial is delivered as planned. We have budgeted for 2 Trial Steering Committee and 2 Data Monitoring Committee meetings each year to include: initiation, post pilot study and with the others to be confirmed and planned following the results of the internal pilot phase.

Month	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36
Oversight												
TMG	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
PPI	x	x	x	x	x	x	x	x	x	x	x	x
TSC/DMEC	x		x		x		x		x			x
Trial												
Set up & approvals												
Training												
Pilot (n)			20	60								
Main trial (n)					96	120	120	120				
Recruitment (n)			20	80	176	296	416	536				
Follow-up												
Analysis												
HTA Report												

8 PROJECT MANAGEMENT

Sponsor and contracting NHS organisation:

The legal sponsor for the trial and contracting organisation will be the University of Warwick. Sub-contracts will be established with NHS partner organisation in accordance with NIHR terms.

Administration:

The study will be coordinated by the UKCRC registered Warwick CTU which has specific expertise in undertaking studies in emergency and critical care. The study will be conducted according to the defined SOPs. The CTU will be responsible for protocol development, ethical and governance approvals, database development and data management, randomisation, trial management and monitoring, analysis of the data and reporting.

Trial management group (TMG):

A Trial Management Group (TMG) chaired by the Chief Investigator (Smyth), supervised by the Co-Chief Investigator (Perkins) and attended by CTU staff, and co applicants will oversee the management of the trial. The TMG will meet face to face and/or by teleconference on a monthly basis. A GANNT diagram will be produced indicating key progress targets / milestones and reviewed at each meeting. Site by site recruitment will be reported to the TMG monthly using the UKCRC endorsed monitoring tool. A dynamic risk assessment will be maintained and reviewed monthly. All the day-to-day activity will be managed by Warwick CTU's full time Clinical Trial Manager working under the direction of the Chief Investigator (Smyth,) who in turn will be supervised by the Co-Chief Investigator (Perkins, Director CTU). This ensures that there is a single point of contact for all enquiries and a single dissemination point for project communications.

Training:

In collaboration with participating Ambulance Trusts, Warwick CTU will develop educational and training material for participating paramedics. These training materials will help standardise recruitment processes,

trial treatments and patient care, and ensure accurate, complete and reliable data are collected. Training will include online learning materials which will remain accessible to participating paramedics throughout the trial, and face-to face instruction. Delivery of face-to-face instruction to participating paramedics at collaborating sites will be the responsibility of each participating Ambulance Trust. 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 protocol and training manual. Training materials including slide shows, videos, FAQs and written material will be available.

Trial steering committee (TSC):

The TSC will provide oversight with respect to the conduct of the study. An independent chair will lead the TSC with at least two other independent members. It will incorporate at least one patient/public representative as well as both co-chief investigators. The TSC roles are outlined in the HTA research governance guidelines as follows: agree proposals for substantial protocol amendments; maintain the rights, safety and wellbeing of participants in the trial; monitor and supervise progress; consider new information relevant to the trial; consider recommendations from DMEC; inform and advise on all aspects of the trial.

Data monitoring and ethics committee (DMEC):

This will comprise 2 independent clinicians with experience in clinical trials and an independent statistician. One of the independent clinicians will have experience in undertaking clinical trials in emergency or acute care. The DMEC charter will be based on the DAMOCLES study group template.[81] Its roles will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies.

9 ETHICS

The study will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki and those in Good Clinical Practice. We will apply separately for ethical approval to a research ethics committee identified for CTIMP trials involving patients without capacity. The ethics application made by the Co-Chief Investigator (Smyth), once approved, will cover all collaborating sites. The trial protocol will be prepared in compliance with the SPIRIT 2013 guidelines.[82] The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register. The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institutions for written approval.

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. We outline our proposed approach to this challenge in the consent section above. 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.[83]

10 PATIENT AND PUBLIC INVOLVEMENT

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 (2 members). We will recruit one young person and one female as additional collaborators in our study to ensure all patient groups are adequately represented

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 (monthly initially and then 3 monthly) 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.

11 PROJECT / RESEARCH EXPERTISE

The trial will be coordinated by Warwick CTU, which has considerable experience conducting randomized controlled trials in prehospital, emergency and critical care settings. This proposal draws together an experienced team of health service researchers with a strong track record in emergency care research. Our team comprises clinician scientists (Smyth (CI), Perkins (Co-CI), Yeung, Fuller), methodologists (Lall (statistics), Petrou and Achana (health economics)) and experienced PPI (Buckley). Smyth, a paramedic and former NIHR Clinical Doctoral Research Fellow will lead the project under the guidance and direct supervision of Perkins (NIHR Senior Investigator and Director Warwick CTU). The trial will be supported by a trained trial manager, trial coordinator, junior statistician and junior health economist, quality assurance manager and a trial assistant.

12 SUCCESS CRITERIA AND BARRIERS TO PROPOSED WORK

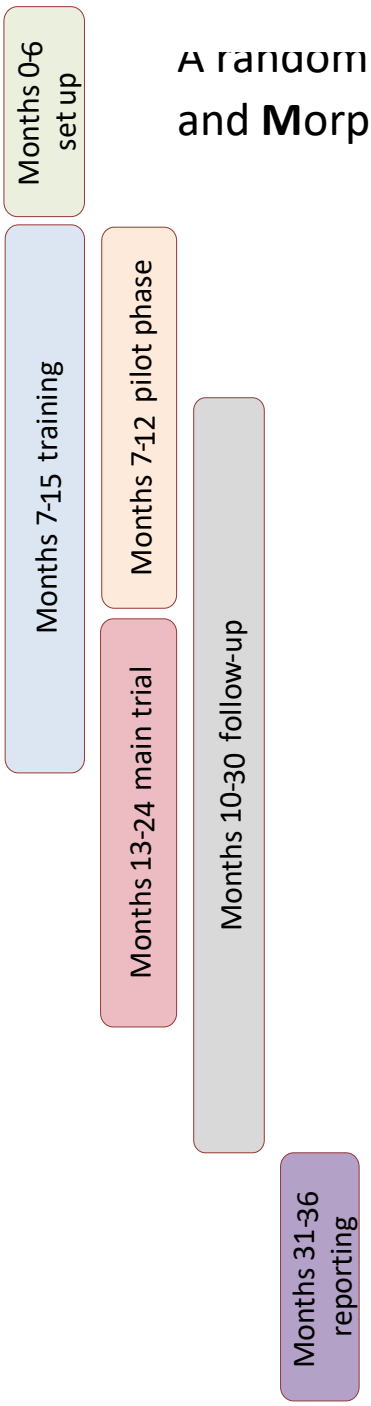
A full risk assessment will be undertaken prior to commencement of the trial and reviewed regularly throughout the conduct of the trial. This will enable a dynamic and on-going assessment and management of risks through the trial.

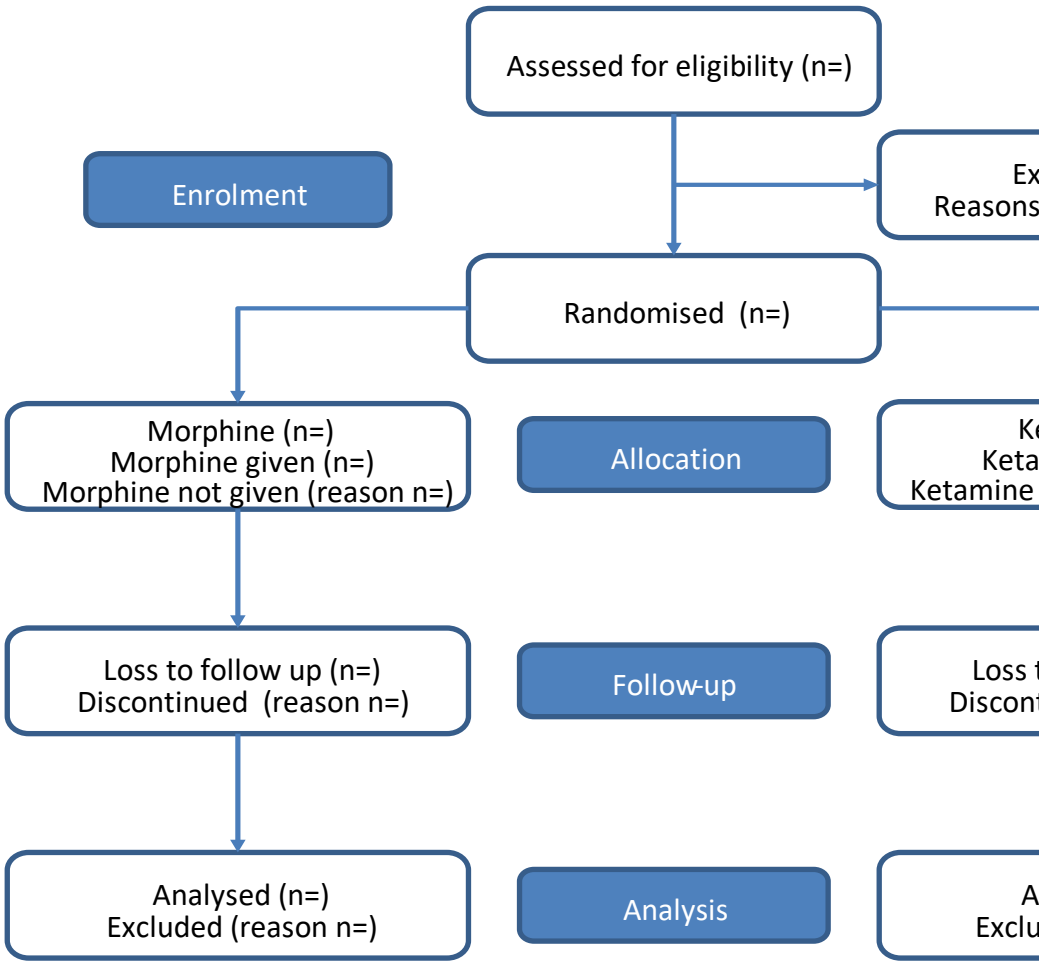
An outline of the key success criteria, barriers and mitigation is presented below.

Success criteria	***Barrier***	***Mitigation***
Ethics and regulatory approval	Difficulty obtaining ethics approval due to lack of capacity among research subjects	Experienced team with track record of designing and delivering research in accordance with the EU / UK Clinical Trials Regulations and ethical standards
Recruitment to time and target	Insufficient infrastructure	Experienced sites with track record of recruiting to trials in prehospital care.
		CRN support

	Recruitment slower than expected	Active site management by WCTU to monitor recruitment and intervene early in event of slower than anticipated recruitment
		Monthly site teleconferences
		Systematic approach to explore barriers to recruitment
	Clinicians do not follow protocol	Co-develop protocol with clinical teams.
		Monitoring and early feedback for non-compliance
		Withdrawal of sites with sustained non-compliance
Complete patient follow-up	Questionnaires not completed	Established system for patient follow-up (letter, phone call, GP contact, support groups)
		Monthly monitoring of return rates by TMG.
		Reporting to TSC meetings

A randomised controlled trial of **P**aramedic **A**nalgesia **C**omparing and **M**orphi**N**e in trauma (PACKMaN)





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A randomised controlled trial of **P**aramedic **A**nalgesia **C**omparing **K**etamine and **M**orphi**N**e in trauma (PACKMaN)

Months 0-6 set up

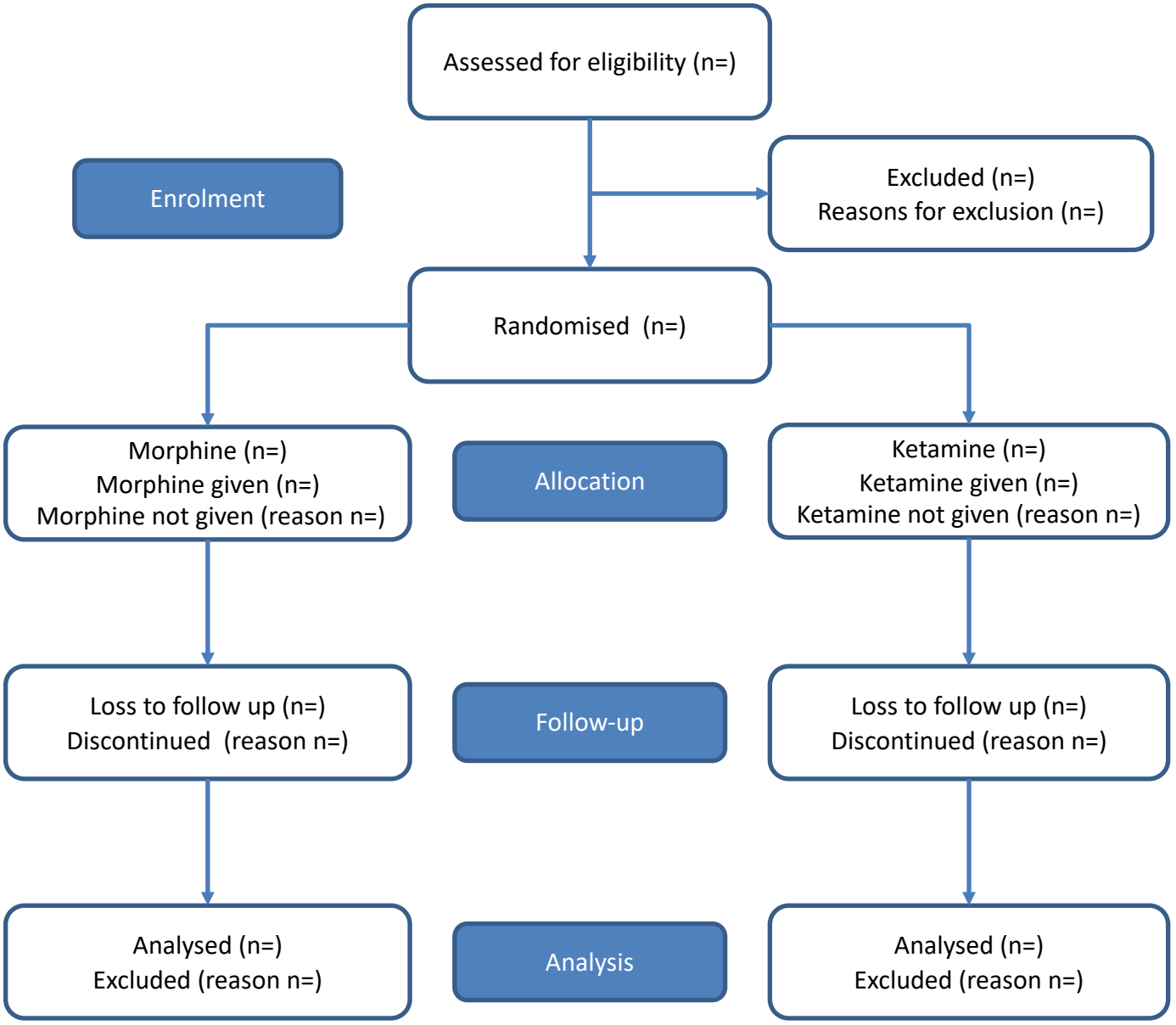
Months 7-15 training

Months 7-12 pilot phase

Months 13-24 main trial

Months 10-30 follow-up

Months 31-36 reporting



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WARWICK

CLINICAL TRIALS UNIT

4 January 2019

National Institute for Health Research
Central Commissioning Facility
Grange House
15 Church Street
Twickenham
TW1 3NL

Dear NIHR HTA

Call: 18/44 Pre-hospital pain management

Full title: A randomised controlled trial of Prehospital Analgesia Comparing Ketamine and Morphine in trauma (PACKMaN)

The Warwick Clinical Trials Unit will be supporting Professor Perkins and Dr Smyth with the above study by providing full trial management.

Yours faithfully,

NStrickland

Natalie Strickland
Head of Operations, Warwick Clinical Trials Unit

Warwick Medical School University of Warwick Coventry CV4 7AL UK
T +44 (0)24 7675 4685
www.warwick.ac.uk

MODEPHARMA
Medication and Services for Clinical Trials

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PROPOSAL					
Project:	Manufacture of Ketamine and Morphine Ampoules, Clinical Trials Packaging, QP Certification, Storage and Distribution for a Non-Commercial 446 Patient Double-Blind Randomised Clinical Trial				
Prepared For:	Dr Mike Smyth Warwick Medical School Clinical Trials Unit University of Warwick				
Offer Number:	MP0625-Q01	**Prepared By:**	Oliver Gupta	**Date:**	06 June 2019

1. INTRODUCTION

Dear Dr Smyth,

Thank you for considering MODEPHARMA for undertaking the manufacture, packaging, labelling and distribution of morphine and ketamine investigational medicinal products for a proposed non-commercial double-blind clinical trial for 446 patients.

Please find enclosed our quotation for the requested services.

High Quality Double-Blind Investigational Medicinal Product Solution:

Under consideration of the dosing schedule and drug products involved we propose a double-blind solution involving:

- Ketamine 15mg/ml (2ml ampoules containing 1ml)
- Morphine 10mg/ml (2ml ampoules containing 1ml)

The ampoules will be terminally sterilised and presented in kits containing 3 ampoules each. The ketamine and morphine ampoules including labelling and packaging will be identical in appearance.

Each ampoule and kit will be labelled in a blinded way according to Annex 13 guidelines with white labels with black text. The labels will have unique kit numbers and the randomisation system will allocate numbered kits to enrolled patients.

Quantities

The following total quantities of kits will be manufactured across 2 manufacturing campaigns:

- Morphine: 335 kits each containing 3 ampoules
- Ketamine: 335 kits each containing 3 ampoules

The quantities above assume an overage of 50%.

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Registered in England & Wales No: 6332969 VAT No: GB 909535016

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Stability and Shelf-life

The proposal assumes that a shelf-life of one year can be assigned to the morphine and ketamine ampoules. In order to support a trial duration of 2 years manufacturing will be undertaken in 2 campaigns.

Samples from ketamine and morphine technical batches will be placed on a real time ambient and accelerated stability study in order to substantiate a minimum expiry date for both ketamine and morphine ampoules. Ideally, we would like to commence this study before Dec 2019 which will provide enough time to collate 3 months stability data which will enable the use of a 12 month expiry date and allow time to apply for the CTA and manufacture clinical batches for delivery for 1st May 2020.

- Real time stability: samples will be pulled and analysed at T=0, 1, 3, 6, 12 and 15 months
- Accelerated stability: samples will be pulled and analysed at T=0, 1, 3 and 6 months

This approach will be explained in the IMPD and is subject to MHRA-approval when applying for the CTA approval.

Project schedule

A 7-month lead time should be assumed for the manufacture of the first IMP campaign after contracts are approved:

- Month 1: Manufacture of technical batch
- Months 2-4: 3-month stability + preparation of IMPD
- Month 5: CTA application
- Month 6: Manufacture and clinical trials packaging of clinical batches
- Month 7: Release testing (1 month), QP release and shipment to site

A 4 month lead time should be assumed for the 2nd manufacturing campaign. At the time of this proposal we are not aware of any manufacturing capacity or raw material sourcing issues.

IMPD and CTA Application Assistance

MODEPHARMA will prepare the Investigational Medicinal Product Dossier (IMPD) for both IMPs providing all relevant technical-pharmaceutical (quality data) information as per regulatory requirements. We will also assist the research team with regards to the label design, IMP-related sections of the protocol and CTA application (IRAS form) to streamline the application process.

QP Release

The active and placebo IMPs will be final QP released for clinical trial use by certifying the conformity of a batch, and the QP will take responsibility that the batch has been produced according to EC-GMP guidelines, Clinical Trial Authorisation and the Product Specification File (Investigational Medicinal Product Dossier).

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Document Deliverables

The following documents will be provided by MODEPHARMA to assist the trial team with the conduct of the trial:

- Technical agreement
- Competent authority GMP and GDP licences
- IRAS form (IMP sections)
- Annex 13 compliant labels
- IMP dossier
- Stability reports
- Certificates of analysis
- QP release certificates
- List of all kit numbers assembled
- GDP-based risk assessment on transport conditions
- Destruction certificates
- Master batch records (upon request).

Storage

Once QP released, the IMP will be stored at the manufacturing site which has a temperature/environmentally controlled storage facility for **controlled drugs**.

Drug Ordering Process

During the setup of the project, a simple email-based drug ordering process will be put in place with the research team. Once a shipment has been dispatched, the trial manager will be informed. All shipments will include an Acknowledgement of Receipt form which is to be completed by the receiving pharmacist and returned to MODEPHARMA.

Dispatch Preparation

We offer fast turnaround times in preparing site shipments from the manufacturing site with hand-over to the courier typically undertaken within 2-3 working days (excluding Fridays to avoid shipping over weekends).

Temperature-Controlled Transportation to Trial Sites

All shipments will be undertaken according to Good Distribution Practice (GDP).

For this project all transfer of IMP whilst under the control of MODEPHARMA will be undertaken under temperature-controlled and temperature-monitored conditions to ensure the quality of the IMPs is not impacted during transport.

Controlled Drug Shipments

All courier shipments are by road, are trackable and MODEPHARMA will manage all aspects of transportation up to the point of delivery to pharmacy.

Shipments to clinical sites will be performed by a vendor-approved courier adhering to delivery of **controlled drug regulations**.

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Prior to clinical distribution taking place, MODEPHARMA will conduct a GDP-based shipment risk-assessment to identify and mitigate any transport-related risks.

Destruction of Expired Products and End of Trial

Any unused trial materials held at the manufacturing site will be destroyed at the end of the trial or after drug expiry after receiving written confirmation from the Sponsor. A destruction certificate will be provided.

Project Fulfilment

Project fulfilment will be undertaken by MODEPHARMA and Huddersfield Pharmacy Specials.

MODEPHARMA is a MHRA-licenced wholesale distributor (WDA(H) 40009) of human medicinal products. MODEPHARMA is also one of the most pro-active and experienced clinical trial medication supply teams in the UK for academic/non-commercial trials.

MODEPHARMA specialises in the diligent planning and organisation of high quality and cost-effective medication for non-commercial clinical trials and studies. Dedicated project managers will work with the trial team to provide full support surrounding the trial IMP and oversee the project to help ensure a smooth execution. Much focus will be placed on the timely fulfilment of GCP, GMP and GDP documentation requirements and the coordination of IMP manufacturing, release and distribution.

We are well-versed with the requirements of this project including IMP manufacture, shelf-life setting, blinded packaging, QP release and distribution of clinical trial supplies particularly in the context of academic/investigator-led clinical trials.

Our clients include:

King's College London
University College London
University of Oxford
University of Warwick
University of Birmingham
Newcastle University
Newcastle Upon Tyne NHS Foundation Trust
University of Bristol
University of Liverpool
Cardiff University
Stockport Pharmaceuticals
University of Nottingham
University of Aberdeen
Royal Brompton & Harefield NHS Trust
St James's Hospital, Ireland
University College Dublin, Ireland
South London & Maudsley NHS Foundation Trust
Northumberland, Tyne & Wear NHS Foundation Trust
Guys' and St Thomas NHS Foundation Trust

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Recent projects including custom-made placebos:

Simvastatin tablets	Levofloxacin film-coated tablets
Metformin tablets	Omega 3 soft gels
Colchicine tablets	Mirtazapine film-coated tablets
Ondansetron tablets and ampoules	Mifepristone tablets
Metoclopramide tablets and ampoules	Donepezil tablets
Methylphenidate bilayer tablets	Doxycyline tablets
Clarithromycin tablets	Lansoprazole capsules
Metronidazole tablets	Minocycline tablets and capsules
Lithium carbonate tablets	Deflazacort tablets
Rituximab vials	Oral Vitamin D3 solutions
Aspirin tablets	Naltrexone tablets
Omalizumab injections	TXA Tranexamic acid
Adrenaline pre-filled syringes	Gardasil(R)
Salmeterol metered dose inhalers (MDI)	Cervarix(R)
Deflazacort tablets	Rituximab (Mabthera)
Prednisone tablets	IVIG
Prednisolone tablets	Melatonin liquids

The project IMPs will be developed and manufactured at Huddersfield Pharmacy Specials which is a NHS Pharmaceutical Manufacturing Organisation specialising in the manufacture and development of sterile and non-sterile investigational medicinal products (IMPs).

HPS has over 40 years experience in developing and manufacturing unlicensed medicines to NHS, community pharmacy, private health care and industry organisations. They operate under an MHRA Investigational Medicinal Products licence (MIA(IMP) 19055) from a modern, purpose-built facility at Calderdale and Huddersfield NHS Foundation Trust, incorporating sterile and non-sterile manufacturing units.

HPS has several years experience with manufacturing ketamine and morphine drug products.

MHRA Licences

MODEPHARMA Limited is a MHRA-licenced wholesaler (WDA(H) 40009) and its subcontractor for GMP activities is a MHRA-licenced MIA(IMP) manufacturer:

MODEPHARMA Limited
Role: IMP project management, regulatory support, IMPD preparation and maintenance, oversight of all IMP planning, manufacturing and distribution, contracts and invoicing
Authorised Site: 114 Barnfield Wood Road, Beckenham, BR3 6SX, UK
MHRA Authorisation: UK WDA(H) 40009

Huddersfield Pharmacy Specials
Role: Manufacture and QP release of IMPs
Manufacturing Site: CALDERDALE AND HUDDERSFIELD NHS FOUNDATION TRUST
MIA(IMP) Authorisation: UK MIA(IMP) 19055

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The appropriate Home Office licence to handle controlled drugs is in place for HPS and will be in place for MODEPHARMA prior to IMP distribution.

Quality Management Systems

MODEPHARMA and its sub-contractor operate according to formal Quality Management Systems consisting of Quality Manuals and Standard Operating Procedures as per current GMP and/or GDP legislation.

Project Management and Reporting of Progress

Throughout the project, a dedicated MODEPHARMA project manager and pharmacist will be your single point of contact with regards to the provision of the tender products/services including:

- the setup of a GMP/GDP Quality **Technical Agreement**;
- the **design of trial medication labels according to Annex 13**;
- **preparation of IMPD for MHRA CTA submission (quality data)**;
- fulfilling documentation requirements according to GCP/GMP/GDP,
- **project management of IMPmanufacturing, supply and distribution and**
- **commercial terms and invoicing**.

Support will be provided via email, phone and face-to-face meetings as required.

The lead project manager assigned to this project is Oliver Gupta. Oliver Gupta is a highly experienced project manager in clinical trial supplies having overseen numerous projects with all of the client organisations listed above. Oliver is the author of the Trial Supplies Station document on the CT Toolkit (NIHR) website: http://www.ct-toolkit.ac.uk/routemap/trial-supplies/

In addition, all communications will be followed by Rima Gupta who is MODEPHARMA's **Clinical Trials Pharmacist and Responsible Person**.

Retention of Records

As per the Standard Operating Procedures of MODEPHARMA, all trial-related documents held by MODEPHARMA will be retained for 30 years. HPS will retain documentation for a minimum period of 10 years from the date of batch release. Based on the sponsor's requirements, a specific retention duration can be agreed or the batch records can be transferred to the Sponsor for archiving after trial completion. The details of the retention times and duties for each party will be formalised in the technical agreement. The documentation will be readily accessible for review and inspection by the sponsor and/or regulatory authorities if requested. After the expiry of the respective periods, all such documentation will be destroyed.

Technical Agreement

A quality technical agreement outlining GMP and GDP responsibilities will be signed between the University, MODEPHARMA and HPS prior to the commencement of the project.

Invoicing and VAT

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Invoices will be issued as per the payment schedule listed in this proposal. As the University of Warwick is a registered charitable organisation and the IMPs are being used for research, **MODEPHARMA can VAT zero-rate the cost of IMP manufacturing** (0% VAT) subject to our acceptance of a VAT exemption certificate and fulfilment of HMRC regulations with regards to zero-rating of medicinal supplies funded by charitable sources. Generally, this does not apply to storage and distribution activities.

Brexit

We have considered the potential impacts of Brexit and do not foresee any potential supply issues as IMP manufacturing, QP release, storage and distribution will be performed in the UK.

Exceptional Client Feedback

We are pleased to share some feedback from our clients:

Trial Manager, University of Oxford	*"You have been an exceptional company to work with."*
Trial Manager, University College Dublin	*"Thank you for all your very professional and prompt support that has been invaluable to us all here."*
Chief Investigator, UCL	*"And thank you for your fantastic support to our trials this year. Your actions over the [NAME with-held] placebo crisis were literally trial-saving!"*
Trial Manager, University of Oxford	*"Thank you for ongoing excellent support with this trial!"*
Chief Investigator, University of Liverpool	*"It has been a pleasure to work with you, and your support has really been outstanding. Thank you for keeping the 'drug-front' quiet for us, so that we were able to focus on recruitment!"*
CTU Manager, Newcastle	*"MODEPHARMA provided a great service. I am very grateful for your time and assistance in getting the CTA application submitted for the study. The support you provided with guidance for IMP related queries was excellent, and was always in a timely manner, which helped us stick to our timelines."*
Trial Manager, King's College London	*"It has been an absolute pleasure working with you and a great comfort knowing that a company such as yours has helped the success of [name withheld].* *Thank you for your help and support throughout the [name withheld] years."*

Further information can be found online: www.modepharma.com/why-use-us

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Please review this proposal and provide any feedback you may have. We would be happy to work with the trial team to further adapt the IMP solution to the trial's requirements.

Yours sincerely,

Oliver Gupta

Director, MODEPHARMA

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2. PROJECT SCOPE OF WORK

Objective:

Prepare technical agreement.

Project set up and prepare project plan.

Prepare Annex 13-compliant labels.

Prepare IRAS form (IMP sections).

Prepare IMP dossier for the CTA application.

Procurement of ketamine and morphine drug substances.

Procurement of 2ml ampoules.

Validate/audit suppliers.

Quality control test ketamine and morphine (identification in line with BP requirements).

Purchase suitable cartons, labels and tamper-evident seals.

Manufacture ketamine 15mg/ml 2ml ampoules containing 1ml fill: manufacture 335 kits of 3 ampoules over 2 manufacturing campaigns.

Manufacture morphine 10mg/ml 2ml ampoules containing 1ml fill: manufacture 335 kits of 3 ampoules over 2 manufacturing campaigns.

Apply randomised Annex 13-compliant labels (white labels with black ink / no tear-off sections) to all ampoules and kits.

Assemble 670 uniquely numbered kits in total over 2 manufacturing campaigns.

Release analysis.

Full QP IMP release and supply of all quality documentation, certificate of conformity, certificate of analysis and QP certificate of release.

Conduct a stability program (under real-time ambient and accelerated conditions) on one technical batch of morphine and ketamine each to confirm a shelf-life of up to 15 months.

Store IMP at 15-25^{o}C in controlled drugs storage.

Undertake multiple temperature-controlled shipments to sites in England as per controlled drugs regulations.

Destruction of unused materials held at the manufacturing site.

Exclusions:

- Randomisation list generation (provided by sponsor). A randomisation schedule will be provided by the sponsor in both an excel spreadsheet and hard copy format.
- Code break envelopes (assumed not required).

All work carried out in accordance with Good Manufacturing Practices and Good Distribution Practices applicable in the UK at the time of manufacturing.

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3. PROJECT COSTING

Item	Quantity	Unit Cost (£)	Cost (£)
IMP Manufacturing - Campaign 1			
Project setup, controlled drugs licence variation	1	11,000	11,000
IMPD preparation and maintenance	1	4,800	4,800
Production setup including batch documentation and technical batches	1	16,500	16,500
IMP manufacturing, labelling, packaging, release testing and QP release	1	23,850	23,850
Stability testing	1	17,800	17,800
IMP Manufacturing - Campaign 2			
IMP manufacturing, labelling, packaging, release testing and QP release	1	23,850	23,850
Sub-total for IMP manufacturing:			**£97,800**
0% VAT on IMP manufacturing:			£0
Storage and Distribution[1]			
Storage per month	24	75	1,800
Dispatch preparation (temperature-controlled boxes)	12	550	6,600
Controlled drugs courier	12	850	10,200
Temperature monitors	12	45	540
Destruction and project close down	1	800	800
Sub-total for storage and distribution:			**19,940**
20% VAT on storage and distribution:			£3,988
Costing Summary:			
IMP manufacturing (incl. VAT @ 0%):			**£97,800.00**
Storage and distribution (incl. VAT @ 20%):			**£23,928.00**
Total (incl. VAT):			**£121,728.00**

4. COSTING NOTES

[1] **Estimate of variable quantities** Unit prices have been provided but the quantity incurred is dependent on the sponsor usage so difficult to predict in advance. Actual usage will be invoiced.

VAT will be charged at the prevailing rate as stated above. IMP manufacturing may be zero-rated subject to our acceptance of a VAT exemption certificate and fulfilment of HMRC regulations with regards to zero-rating of medicinal supplies funded by charitable sources.

Costs in this proposal are valid up to 31 Dec 2019.

Any additional services will be charged at the appropriate rates.

Changes to the scope of work are possible but subject to a change order listing any impacts on the project costing and timeline.

The following costs are excluded as they are not deemed necessary at the time of preparing the proposal:

- Randomisation list generation: to be provided by the sponsor.
- New supplier audits: currently not deemed as necessary.
- Standard materials and equipment are deemed as sufficient, if any project-specific materials, equipment, cleaning or process validations are needed these will be quoted

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separately and may affect the timeline

- Additional cleaning verification work if current procedure is not deemed sufficient.
- Costs for postponement/termination of manufacturing campaigns by the University that have already been confirmed.
- Returns from clinical sites. It is assumed that clinical sites can destroy returned IMP more cost efficiently.

5. PAYMENT TERMS	
Payment:	BACS transfer within 30 days of the date on an interim or final invoice.
Banking Details:	Name of Account Holder: MODEPHARMA Bank: Barclays Account Number: 93489426 Bank sort code: 20-14-33 SWIFT/BIC code: BARCGB22 IBAN Number: GB68 BARC 2014 3393 4894 26 Bank Address: Barclays, 167 High Street, Bromley BR1 1NL, England Please provide remittance details to billing@MODEPHARMA.com. Any applicable bank transfer fees and/or currency conversion fees must be included in the payment issued to MODEPHARMA.
Invoicing issuance:	MODEPHARMA will issue invoices as follows: Payment schedule Campaign 1: £15,800 at project start, £16,500 at commencement of stability study, £11,925 at start of manufacturing, £29,725 at QP release, Campaign 2: £11,925 at start of manufacturing and £11,925 at QP release Storage and distribution: monthly as incurred

6. STANDARD TERMS AND CONDITIONS

Refer to the attached terms and conditions.

7. TIMELINE

Once the project has been awarded to MODEPHARMA and the relevant documentation and deposit payment are in place, a detailed timeline detailing set milestones and duration of deliverables will be agreed upon between the Sponsor and MODEPHARMA. The timeline will be based upon resources and the availability of manufacturing time at the initiation of the project.

8. CLIENT SUPPLIED DOCUMENTATION

In order to perform this project, the client will provide the following documentation:

- Signed quotation approval page and VAT exemption certificate (if applicable).
- Signed technical agreement.
- Treatment pack allocation list (electronic form and hard copy).
- Details of the emergency unblinding service to be used in the trial.

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- Study protocol.
- CTA and Ethics acceptance letter and amendments.

9. REGULATORY MANUFACTURING REQUIREMENTS

- All pharmaceutical services are carried out in accordance with the current Good Manufacture Practices and Good Distribution Practices.

10. QUALITY TECHNICAL AGREEMENT

- This project will be performed under the terms of a Quality Technical Agreement which outlines the roles and responsibilities between the Sponsor, MODEPHARMA and Huddersfield Pharmacy Specials relating to technical and operational responsibilities with regards to the provision of pharmaceutical manufacturing (GMP) and distribution (GDP) services.
- The Technical Agreement will be agreed with the Sponsor prior to any manufacturing being undertaken.

11. PROJECT SUPPORT

- MODEPHARMA will provide project management support to monitor the progress of the project against established timelines and will provide the Client with updates.
- Throughout the project, a MODEPHARMA project manager will coordinate with the Client's project team with regards to the arrangement of the study medication and provide support via email, phone and face-to-face meetings when requested.
- The fees for project management are incorporated in the project costing.

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Quotation Approval

I accept the quote as submitted by MODEPHARMA as detailed above. I understand that any changes made once this quote has been accepted can result in additional charges being incurred.

Signed: _____ **Date:** _____

Name: _____ **Position:** _____

(Block Capitals)

Sponsor:

Organisation: _____

Address: _____

_____

Representative:

Name: _____

Position: _____

Tel: _____

Email: _____

Purchase Order Number:
Please provide us with a Purchase Order (PO) Number as our finance department requires one. This will then by entered on the invoice.

PO Number: _____ **Accounts Contact:** _____

Tel: _____ **Email:** _____

VAT Exemption:
Acceptance of VAT zero-rating is subject to MODEPHARMA's approval of a completed VAT exemption certificate.

Please sign and return a copy of the Quotation Approval page via either of the following:

1. **Fax to MODEPHARMA at +44 (0) 207 0432 412**
2. **Email to MODEPHARMA at info@modepharma.com**

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Terms and Conditions

1. APPLICABILITY

A. These Terms and Conditions constitute a part of the quotation/proposal/offer to which they are attached and the Buyer purchase order (collectively, "this Agreement") between MODEPHARMA on the one part (hereinafter referred to as “the Seller”) and the UNIVERSITY OF WARWICK on the other part (hereinafter referred to as “the Buyer”). These Terms and Conditions supersede in their entirety the terms and conditions set forth in the quotation/proposal/offer to which they are attached and supersede any conflicting terms and conditions set forth in any Buyer purchase order.

B. This Agreement governs the commercial terms and conditions of the Buyer’s and Seller’s cooperation applying to the supply of goods and/or services (hereafter referred to as the “Goods”) set forth in the Buyer’s purchase order. Technical roles and responsibilities with regards to the provision of medicinal products are governed in a separate Technical Agreement (herein referred to as the “Technical Agreement”) between the Buyer and the provider of the medicinal product which may be the Seller or a designated third party.

C. If any provision of this Agreement is held by any competent authority to be invalid or unenforceable in whole or in part, the validity of the other provisions of this Agreement and the remainder of the provision in question shall not be affected.

D. Words importing the singular include the plural and vice versa, words importing a gender include every gender and references to persons include bodies corporate or unincorporated.

E. The headings to the clauses are for convenience only and have no legal effect.

2. DELIVERY

A. Goods shall be delivered at the time stated in the Buyer’s purchase order. Where time of delivery is not specified or delivery not made at such time, the Buyer may by 28 days notice to the Seller make time of the essence as at the date fixed by such notice.

B. The Seller shall give the Buyer reasonable written notice of any foreseeable delay in the execution of purchase orders.

C. If the parties have agreed for the Seller to arrange the transport of the Goods, the Seller shall choose the nature of the transport, which shall be appropriate to the Good being delivered and in accordance with applicable laws and regulations.

D. Where required, as the case may be, the Seller shall ensure the existence of adequate transportation insurance prior to each shipment.

E. The Seller shall, at its own expense, ensure that the Goods are properly packed, secured and despatched in order that they are delivered to the Buyer in good condition and free from any damage.

F. The Goods shall be delivered to the address stated by the Buyer in the Buyer purchase order on the date or within the period stated in the purchase order, or as otherwise reasonably notified to the Seller in writing, in either case during usual business hours. The Buyer shall receive the Goods when delivered. If the Buyer does not receive the Goods in accordance with its obligations under this Agreement or otherwise there is any delay in supply and shipment solely as a result of the Buyer, the Seller shall be entitled to store the Goods until delivery can take place, with any reasonable storage costs incurred for the Buyer’s account. Upon the Buyer’s delay of supply and shipment within the Buyer’s sole responsibility, risk shall pass to the Buyer with the Seller’s notification of readiness for shipment and the Seller shall be entitled to invoice the according orders. This does not affect the Seller’s claims from the Buyer’s default on acceptance. If after the expiry of a limited storage period that is deemed to be reasonable in view of the type of product, no receipt by the Buyer has taken place and the risk of quality loss and/or deterioration of the Goods leaves the Seller no choice, he shall be entitled - if

still possible - to sell said Goods. In that case the possible price difference resulting from said sale, and reasonable direct costs, damage and loss incurred by the Seller shall be borne by the Buyer.
G. If the Goods or any part of them are not delivered by the time or times specified in the purchase order or as otherwise reasonably agreed in writing between the Parties, then the Buyer may by written notice cancel any undelivered balance of the Goods.

H. Where the Seller fails to deliver any Goods at the correct time or place, the Buyer shall be entitled to deduct from the price of the Goods in question any costs incurred in respect of storage or transport of such Goods.

I. The Buyer shall be entitled to reject any Goods delivered which are not in accordance with the Agreement or the Technical Agreement, and shall not be deemed to have accepted any Goods until the Buyer has had a reasonable time to inspect them following delivery or performance or, if later, within a reasonable time after any latent defect in the Goods has become apparent.

3. TITLE AND RISK

A. Title to the Goods shall pass to the Buyer at the time of payment, provided that such passing shall not prejudice the Buyer's right to reject for non-conformity with the Agreement or the Technical Agreement and shall not prejudice any other rights that the Buyer may have under the Agreement.

B. Risk in the Goods shall pass to the Buyer upon delivery of the Goods to the address stated by the Buyer in the purchase order or as otherwise agreed between the Parties in writing.

C. The Buyer shall be obliged to inform the Seller forthwith of any actions taken by third parties with respect to Goods belonging to the Seller.

D. Until payment for the goods has been made, the Buyer shall be obliged to store the Goods delivered under retention of title carefully and as the identifiable property of the Seller.

E. Following delivery of the Goods to the Buyer, it shall be the Buyer responsibility to ensure adequate insurance is in place in relation ot he Goods.

4. PRICES

A. The quoted prices for the Goods shall apply only if the whole offer is accepted.

B. The Seller may reasonably revise the prices if the Buyer's requirements or any Buyer-provided information is inaccurate or incomplete or if the Buyer revises the Seller's responsibilities or the Project specifications, instructions, procedures, assumptions, processes, test protocols, test methods or analytical requirements.

C. Unless otherwise stated or agreed upon, all prices are net, therefore exclusive of Value Added Tax, sales tax, other taxes, government levies and transport costs which shall be the responsibility of the Buyer.

D. All prices are based on the official monetary relationships of domestic and foreign currencies, on import duties, prices of raw materials and energy, other taxes and levies valid at the time of the offer.

E. In the event of a price-increase before delivery of one or more of the factors referred to under article 4D, the Seller reserves the right to increase his prices such that said increase(s) is/are allowed for in a reasonable way.

F. The Seller shall inform the Buyer in writing of any price increase specified in Clauses 4.B and 4.E. If the Buyer does not agree with the price increase, the Buyer will without prejudice to its rights under this Agreement or in law be entitled to terminate the Agreement with regard to the remaining part, within five working days after the receipt of the price increase notice.

5. BUYER OBLIGATIONS

A. Unless otherwise agreed to by the parties in writing, the Buyer is solely responsible to (i) provide complete and accurate scientific data regarding the work to be undertaken; (ii) if applicable, review and approve all in-process and finished product test results to ensure conformity of such results with the product specifications, regardless of which party is responsible for finished product release; (iii) prepare all submissions to regulatory authorities; and (iv) perform such other obligations of Buyer set forth in this Agreement.

B. The Buyer shall place purchase orders in writing. Amendments, endorsements, extensions and the like of individual orders must also be in writing.

C. In addition to the Buyer's other rights of cancellation under this Agreement and in law, the Buyer may cancel the purchase order and any order amendment thereto by sending a notice of cancellation to the Seller at any time. The Seller will immediately comply with any instructions issued by the Buyer in respect of the Goods. If the Seller submits a termination claim then the Buyer will pay to the Seller reasonable cost of any commitments, liabilities or expenditure, including financial obligations of the Seller towards third parties, which in the Buyer's reasonable opinion relate to the cancellation of the Agreement and that the Seller still needs to meet, which were a consequence of this Agreement at the time of termination, provided that the Seller has used its best endeavours to reduce and mitigate all such costs. For the avoidance of doubt the Buyer shall not be liable for any payments in relation to any orders which had not been placed prior to the date of termination. The total of all payments made or due to the Seller in connection with cancellation under this Clause shall not exceed the purchase price of the Goods as set forth in the Buyer purchase order. If the Seller fails to submit a termination claim within three (3) months of the date of the Buyer's notice of termination then the Buyer shall have no further liability under this Agreement.

6. INVOICING AND PAYMENT

A. The Seller shall submit invoices to the Buyer as set forth in this Agreement in a form of a valid VAT invoice.

B. The Buyer undertakes to pay the invoice within thirty (30) days of receipt in the manner indicated by the Seller wherever reasonable, unless otherwise agreed in writing.

C. In the event of any dispute regarding the invoice, the Buyer must inform the Seller in writing within seven (7) days of receipt of the invoice.

D. The Buyer shall be in default by the simple expiry of the payment term, without any notice of default being required. If payment is not received by the Seller on or before the due date the Seller shall be entitled, without limiting any other rights it may have to:

I. Cancel the Agreement or suspend the provision of any further services to the Buyer;

II. Accelerate the time for payment of all outstanding invoices so that they are all due and payable;

III. Appropriate any payment made by the Buyer to such invoices as the Seller may think fit (notwithstanding any proportion of appropriation by the Buyer);

IV. Charge interest on the outstanding amount (both before and after judgment) at the rate of 3% above the lending rate of Barclays Bank from the due date until the outstanding amount is paid in full;

V. Retain and exercise a lien over any Goods in its possession belonging to the Buyer until outstanding invoices have been settled in full; and

VI. the Buyer shall be obliged to reimburse reasonable judicial and extrajudicial collection costs, including all reasonable costs incurred by the Seller for attorneys-at-law, lawyers, process-servers and debt-collecting agencies.

E. Failure to bill for interest due shall not be a waiver of the Seller's right to charge interest.

7. REGULATORY INSPECTIONS AND GOVERNMENT IMPEDIMENT

A. Both parties will promptly notify the other party of any regulatory inspections directly relating to the provision of the Goods. The Buyer accepts reasonable and documented costs charged by a regulatory authority for inspections which are conducted in relation to the Buyer or in relation to the trial being undertaken by the Buyer.

B. The Seller warrants that to the best of its knowledge at point of purchase the Goods supplied to the Buyer comply with all applicable laws and regulations. After receipt of the Goods by the Buyer, should the Seller become aware that any of the goods cease to become compliant or that any law or regulation has been or has come into force preventing or prohibiting the use of the Goods in whole or in part, the Seller shall inform the Buyer immediately in writing. Upon receipt of such notice, the Buyer will take such action as is necessary to ensure compliance with the applicable laws and regulations. The Buyer shall bear the risk of regulations by the authorities or by any other competent body that prevent or prohibit the use of Goods (including product recalls) supplied by the Seller, provided that such non-compliance was not due to the acts, omissions and negligence of the Seller, APL, or resulted due to the manufacture of the Goods.

8. NON-FULFILMENT AND TERMINATION

A. In the event of the filing of a petition for bankruptcy, bankruptcy, provisional attachment, statutory debt rescheduling, liquidation or in the event that a suspension of payments of the Buyer was applied for or granted, the Seller shall be entitled to terminate the Agreement unilaterally by registered mail without any notice of default and without any judicial intervention or to suspend the execution thereof in whole or in part without being liable to pay compensation and without prejudice to any other rights to which it is entitled.

B. If one of the circumstances referred to in Clause 8.A occurs on the part of the Buyer, all amounts outstanding of the Buyer by virtue of any legal relationship shall immediately be due in full and the Seller shall also be entitled to suspend or terminate all other agreements with the Buyer.

C. The Seller shall in the same way as referred to under Clause 8.A be entitled to suspend the obligations or to terminate the Agreement, if:

I. the Buyer breaches its obligations under this Agreement (provided that the Seller has given the Buyer fourteen (14) days from receipt of notice from the Seller to correct the breach); and/or

II. as a result of the delay on the part of the Buyer, the Seller can no longer be expected to fulfil the Agreement at the conditions originally agreed upon, provided that the Seller has made all reasonable efforts to fulfil its obligations under the Agreement despite the delay.

D. At the application of Clauses 8.A, 8.B and/or 8.C, the Buyer's liability to the Seller shall not exceed the maximum the price paid by the Buyer for the provision of the Goods under this Agreement.

E. The Agreement may be terminated at any time on written notice from the Buyer if:

I. the Seller, in the reasonable opinion of the Buyer, breaches any of terms of the Agreement, either in relation to provision of the Goods or otherwise (provided that the Buyer has given the Seller seven (7) days from receipt of notice from the Buyer to correct the breach); or

II. the Seller, being an individual, or, where the Seller is a firm, any partner in that firm shall at any time become bankrupt, or shall have a receiving order, administration order or interim order made against him, or shall make any composition or scheme of arrangement with or for the benefit of his creditors, or shall make any conveyance of assignment for the benefit of his creditors, or shall purport to do so, or if in Scotland he shall become insolvent or notour bankrupt, or any application shall be made for sequestration of his estate, or a trust deed shall be granted by him for the benefit of his creditors; or has a receiver appointed under the Mental Health Act 1983, dies or by reason of any illness (including

mental disorder or infirmity), accident or injury or any other cause whatsoever becomes unable to comply with its obligations under the Agreement;

III. the Seller has any distraint, execution or other process levied or enforced on any of its property;
IV. the Seller ceases, or appears in the reasonable opinion of the Buyer likely or is threatening to cease to trade;
V. the Seller being a company shall pass a resolution, or the Court shall make an order, that the company shall be wound up (except for the purpose of amalgamation or reconstruction) or if a receiver, manager, administrator or administrative receiver is appointed (or steps have been take to appoint) over any of its assets, undertakings or income, or if the Court shall make an administration order, or if circumstances shall arise which entitle the Court or a creditor to appoint an administrative receiver or which entitle the Court to make a winding-up order or administration order or if the Contractor shall be the subject of a notice to strike off the register at Companies House;

VI. the trial is halted on the grounds of participant safety or the regulatory approvals are withdrawn and the Goods are no longer required.

VII the Goods are subject to a product recall

provided always that such termination shall not prejudice or affect any right of action or remedy which shall have accrued or shall accrue thereafter to the Buyer.

F. Without prejudice to its rights under this Agreement or in law, the Buyer shall be entitled (whether or not the Goods or any part thereof have been accepted by the Buyer) to avail itself of any of the following remedies at its sole discretion:

I. rescission of the Agreement; or

II. giving the Seller the reasonable opportunity at the Seller's sole cost and expense to enable the Goods to comply with the terms of the Agreement; or

III. refusing to accept any further provision of the Goods without any liability to the Seller; or

IV. claiming such damages, costs and expenses as the Buyer may have sustained in consequence of any breach of the terms of the Agreement or failure by the Seller to comply with any statutory or other legal obligations herein specified or implied by law.

These rights shall be in addition to and without prejudice to any other rights the Buyer may have.

9. FORCE MAJEURE

A. If, by any reason of any act or default of the Buyer or any other circumstance which is beyond the reasonable control of the Seller arising after the date of this Agreement (which shall include, but not be limited to, acts of God, perils of the sea or air, flood drought, explosion, sabotage, accident, embargo, war, riot, civil commotion, including acts of local government or parliamentary authority and/or labour disputes (other than labour disputes, strikes or lock outs involving the Seller's own personnel and workforce and/or staff employed by the Seller), including restrictive government measures of any kind, the not timely or not properly functioning of third party installations used for the execution of this Agreement and the failure in whole or in part of a third party to supply goods, the Seller has been delayed or impeded in the completion of the Agreement, and provided that the Seller shall immediately have given to the Buyer notice in writing of its claim for an extension of time or termination of the Agreement, the Buyer shall upon receipt of such notice either terminate the Agreement in whole or in part without judicial intervention, or to suspend it or grant the Seller from time to time in writing either prospectively or retrospectively an extension of time for the completion of the Agreement as may be reasonable, but which shall not, unless otherwise agreed between the parties in writing, exceed sixty (60) days after the date of the Seller's notice to the Buyer as set out above. This Clause only applies if:

I. the Seller shall, immediately upon becoming aware that such delay has been or is likely to be caused, give notice in writing to the Buyer specifying the circumstances causing or likely to cause the delay and the actual or estimated extent of the delay caused or likely to cause the delay;

II. the Seller could not reasonably be expected to have foreseen at the date of the Agreement that a delay would, or was likely to, occur;

III. the Seller uses its best endeavours to prevent any delay being caused and to minimise any such delay to the satisfaction of the Buyer; and

IV. such delay is not attributable to any negligence, default or improper conduct of the Seller.

B. If the Buyer has granted the Seller an extension of time as set out in Clause 9.A, and the Agreement is not concluded within the extended period, the Buyer may by giving notice to the Seller terminate the Agreement with immediate effect. Termination of the Agreement under this Clause 9.B shall be without prejudice to any rights which may have accrued to the Buyer to the effective date of such termination.

10. LIABILITY, WARRANTY AND COMPLAINTS

A. The Seller warrants to the Buyer that the Goods:

I. will be of the highest quality, in line with best industry standards and fit for their normal purpose and any other purpose held out by or known to the Seller at the time the purchase order is placed, and in this respect the Buyer relies upon the Seller's skill and judgment;

II. will be free from defects in design, material and workmanship;

III. will correspond with any relevant specification, quantities, standards of performance, stipulations or samples provided in the Agreement;

IV. will comply with all statutory requirements and regulations relating to the sale of the Goods; and

V. shall not contain any asbestos or asbestos based products, unless specifically required in the Agreement.

B. With the exception of the application of mandatory law, both parties can only be held liable for loss or damage that is attributable to their intent or negligence. No liability whatsoever shall be incurred by either party for consequential damage or trading loss, indirect damage and loss of profits or turnover.

C. Neither party shall have any liability to the other for any loss, damage, costs, expenses or other claims for compensation arising from any error or omission in the information and instructions supplied by the other party which are incomplete, incorrect, ambiguous, illegible, out of sequence or in the wrong form, or arising from their late arrival or non-arrival.

D. The Seller does not make any representations or warranties regarding any therapeutic or pharmacological effects, results and/or characteristics of the Goods.

E. I. The Buyer shall be obliged to inspect the goods out of their original packaging at the receipt thereof, or otherwise as soon as possible before use. Any complaint about the Goods shall be submitted to the Seller in writing within seven (7) days after receipt of the Goods delivered, or within seven (7) days after the time the defect could reasonably have been discovered, stating reasonable ground(s), the number and date of the relevant order confirmation/invoice.

II. The Buyer shall take steps in order to limit the damage to Goods delivered as much as is reasonably possible and within its reasonable control.

III. The Buyer shall strictly observe the provisions regarding the storage and handling of the Goods delivered provided that the Seller has provided this information to the Buyer in writing as soon as possible prior to purchase order.

IV. The Buyer shall give the Seller reasonable opportunity to investigate a possible reported defect with the goods.

V. The Seller shall have no liability to the Buyer in connection with damage to the Goods if such damage results from the Buyer's failure to meet the provisions referred to in Clauses 10.E.II, 10.E.III or 10.E.IV.

VI. The Seller shall also have no liability in respect of damage to the Goods, if such damage is caused by or results from injudicious or improper use or use after the expiry date, incorrect storage or maintenance by the Buyer and/or by third parties acting on behalf of the Buyer or, if, without written consent of the Seller, the Buyer or third parties acting on behalf of the Buyer made alterations to the goods or attempted to alter these, or if these were processed or treated in another than the prescribed way. The Seller shall also have no liability for damage to the goods following acceptance of the goods by the Buyer, if such damage arises from or is the result of circumstances that the Seller cannot influence, including weather conditions (including, but not limited to, extreme temperatures).

F. Without prejudice to the Buyer's right of rejection under this Agreement and in law, the Seller shall settle complaints properly submitted and reasoned by being obliged to provide to the Buyer either a full refund of the price paid for the Goods, an additional supply of the Goods that were short-delivered, a replacement of the Goods for Goods of equivalent specification, or a reduction of the price for that portion of the Goods subject to the complaint where a portion of the Goods are affected. The Seller will never take back, replace or credit Goods with a limited storage period after the expiry of said period provided that when the Goods are received by the Buyer there is a reasonable time before the expiry of said period such that the Buyer's normal rights of rejection are not affected. If the Seller is able to prove a complaint is unfounded, any reasonable costs including research costs incurred on the part of the Seller for investigating the complaint shall be at the expense of the Buyer. The Seller's expenses, fees, and other costs in connection with any complaint shall be limited to and shall not exceed the amount of the individual order value wherever possible provided that such limitation shall not prevent the Seller from fulfilling its obligations under this Clause.

G. After the Seller has failed specific performance twice, the Buyer may at its discretion withdraw its purchase order (in which case the Seller will be obliged to refund the Buyer in full) and may claim damage compensation.

11. INTELLECTUAL PROPERTY AND CONFIDENTIALITY

A. Both parties to this Agreement acknowledge that to the best of their knowledge and after reasonable investigation, none of the Goods, services, products, materials or anything else provided by it to the other in order to execute this Agreement infringes the intellectual property rights of any third parties.

B. Where a third party makes a claim of infringement or alleged infringement of intellectual property rights by the use or possession of any Goods, services, products, materials or anything else provided by one of the parties to this Agreement to the other party in order to execute this Agreement, the party which has provided the Goods, services, products and/or materials subject to the intellectual property claim shall indemnify the other party from any such third party claims (to a maximum in the aggregate the amount paid by the Buyer to the Seller under this Agreement, in connection with each of the parties) provided that:

I. both parties shall promptly notify the other in writing of any alleged infringement of which they have notice;

II. neither party shall make any admissions without the other's consent;

III. the party which has provided the goods, services, products or materials subject to the claim shall at its request and its sole cost and expense be allowed by the other party to conduct and/or settle all negotiations and litigation.

C. The Seller and the Buyer shall observe strict secrecy with regard to all information and/or data regarding their reciprocal business operations and shall not disclose this to third parties in any way whatsoever, unless this information and/or these data was/were already demonstrably facts of general knowledge at the date of the Agreement between the Seller and the Buyer, or unless one party granted the other party permission in writing to disclose this information and/or these data to a third party/third parties, or unless required to disclose such information by a statutory requirement or by a court order.

12. SUBCONTRACTING

A. The Seller reserves the right to subcontract all or part of its services entrusted to it if it cannot carry out said services itself, provided it notifies the Buyer in writing prior to subcontracting the services.

13. HARDSHIP CLAUSE

A. If during the term of this Agreement the circumstances that the parties departed from at the date of this Agreement change so fundamentally, that compliance with one or more provisions cannot reasonably be expected any longer, the parties shall use reasonable endeavours to negotiate an interim amendment of the Agreement.

14. INDEMNITY

A. The Buyer shall indemnify the Seller against any third party claim arising directly from the negligence or wilful misconduct of the Buyer or the breach of this Agreement by the Buyer. The Buyer shall also indemnify the Seller against possible claims from third parties, who in connection with the execution of this Agreement suffer damage directly from the use of the Goods, unless the cause is attributed to the Seller and/or any party acting on behalf of the Seller. Any indirect or consequential loss suffered by any party is expressly excluded and the Buyer shall have no liability in this regard.

B. If an action is brought against either party in connection with this Agreement, the other party shall provide it with such reasonable assistance as may be required. If such assistance is not forthcoming then the other party shall be entitled to proceed hereto itself without any notice of default.

C. The Seller will indemnify the Buyer against any third party claim arising directly from the negligence or wilful misconduct of the Seller or the breach of this Agreement by the Seller.

D. The Seller shall indemnify the Buyer against all costs or expenses incurred by the Buyer in relation to the collection, destruction and manufacture of the Goods as a result of any product recall relating to a defect or fault in the manufacture of the Goods.

E. Both parties to this Agreement will take out and maintain such insurance policies as are necessary to meet their potential liabilities under this Agreement and shall, upon the request of the other party, provide evidence of the insurance policy or policies and of payment of the premiums.

15. RECISSION OF OTHER AGREEMENTS

A. This Agreement is in substitution of all previous agreements for the Goods between the Buyer and the Seller which shall be deemed to have terminated by mutual consent as from the date of this Agreement.

16. WAIVER

A. No indulgence granted by a party shall constitute a waiver of any of that party's rights under this Agreement; accordingly, that party shall not be precluded, as a consequence of having granted such indulgence, from exercising any rights against the other which may have arisen in the past or which may arise in the future.

17. VARIATION AND CANCELLATION/ ENTIRE AGREEMENT

A. No agreement varying, adding to, deleting from or cancelling the Agreement shall be effective unless in writing and signed by or on behalf of the parties. The Agreement sets out the entire agreement and understanding between the Buyer and the Seller in relation to its subject matter and neither party has entered into the Agreement in reliance upon any representation, warranty or undertaking which is not set out or referred to in the Agreement.

18. NOTICES

A. Notices by either party shall be given in writing and may be delivered personally or sent by letter addressed to the other party at its registered office for the time being. Any such notice given by letter shall be deemed to have been given seven days after posting if sent by post and on the date of delivery if delivered personally.

19. DISPUTE RESOLUTION

A. If a dispute arises between the parties in connection with this Agreement, the respective authorised representatives of the Seller and the Buyer shall first attempt to resolve the dispute. If the parties cannot resolve the dispute, such dispute shall be subject to the exclusive jurisdiction of the English courts, without reference to principles of conflicts of laws. The application to the United Nations Convention on the Sale of Goods (1980) is excluded.

20. JURISDICTION

A. This Agreement shall be interpreted and governed in accordance with the laws of England and Wales and parties hereby submit to the exclusive jurisdiction of the English Courts.

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Registered in England & Wales No: 6332969 VAT No: GB 909535016

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Professor Stavros Petrou
Role and organisation	Professor of Health Economics
Department	Clinical Trials Unit
Organisation	University of Warwick
Email	S.Petrou@warwick.ac.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
PhD - Health Economics	University of St Andrews - 30/09/1991
MPhil - M.Phil in Management, Economics and Politics	UNIVERSITY OF ST. ANDREWS - 30/09/1988
BSc (Hons) - Economics	UNIVERSITY COLLEGE LONDON - 30/09/1987

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	5 % FTE

Recent Relevant Publications

Costa ML, Achten J, Bruce J, Davis S, Hennings S, Willett K, Petrou S, Jeffery S, Griffin D, Parker B, Masters J, Lamb SE, Tutton E, Parsons N. UK Wound management of Open Lower Limb Fractures (UK WOLLF) – A randomised controlled trial and health economic evaluation of standard wound management versus negative pressure wound therapy in the treatment of adults with an open fracture of the lower limb. Health Technology Assessment, in press.

Petrou S, Kupek E. Epidemiological trends and risk factors for tobacco, alcohol and drug use among adolescents in Scotland, 2002-2013. Journal of Public Health, in press. doi: 10.1093/pubmed/fdy006.

Petrou S, Kwon J, Madan J. A practical guide to conducting a systematic review and meta-analysis of health state utility values. PharmacoEconomics 2018; 36(9): 1043-1061. doi.org/10.1007/s40273-018-0670-1

Petrou S, Yiu HH, Kwon J. The economic consequences of preterm birth: A systematic review of the recent literature (2009-2017). Archives of Disease in Childhood, in press. doi: 10.1136/archdischild-2018-315778.

Costa ML, Achten J, Bruce J, Tutton E, Petrou S, Lamb SE, Parsons N, on behalf of the UK WOLLF collaboration. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: The WOLLF randomised clinical trial. JAMA: The Journal of the American Medical Association 2018; 319(22): 2280-2288. doi:10.1001/jama.2018.6452.

Perkins GD, Ji C, Deakin C, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M, Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R, on behalf of PARAMEDEIC2 collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. New England Journal of Medicine 2018; 379(8): 711-721. doi: 10.1056/NEJMoa1806842.

Research Grants Held

Title: WAX: Weight-bearing in ankle fractures. A randomised clinical trial of weight-bearing following operatively treated ankle fracture. (Health Economics Lead and Co-Investigator)

Total: £349,570

Source of grant: National Institute for Health Research, Research for Patient Benefit Programme

Duration: 2019-2022

Lead investigator: Mr Xavier Griffin (Oxford)

Other investigators: Dr Henry Claireaux (Oxford), Mr Christopher Bretherton (Oxford University Hospitals NHS Foundation Trust), Dr Juul Achten (Oxford), Mrs Susan Dutton (Oxford), Dr Rebecca Kearney (Warwick), Dr Philip Bell (PPI representative), Dr Duncan Appelbe (Oxford)

Title: The clinical and cost effectiveness of screening for Group B Streptococcus (GBS) in pregnancy.

(Health Economics Lead and Co-Investigator)
Total: £2,886,042
Source of grant: National Institute for Health Research Health Technology Assessment Programme
Duration: 2019-2022
Lead investigator: Prof J Daniels (Nottingham)
Other investigators: Dr K Walker (Nottingham), Dr J Gray (Birmingham), Prof S Ayers (City), Dr R Ogollah (Nottingham), Ms E Mitchell (Nottingham), Dr J Dorling (Nottingham), Prof J Thornton (Nottingham), Ms J Plumb (Group B Streptococcus Support), Prof S Downe (Central Lancashire), Dr V Taylor (NHS England), Ms D Parry (NCT), Dr T Cooper (Warrington and Halton Hospitals NHS Foundation Trust).

Title: An online parenting intervention to prevent affective disorders in high-risk adolescents: The PIPA trial. (Health Economics Lead and Co-Investigator)
Total: £1,279,170
Source of grant: National Institute for Health Research Public Health Research Programme
Duration: 2019-2022
Lead investigator: Dr A Thompson (Warwick)
Other investigators: Prof M Birchwood (Warwick), Dr J Warwick (Warwick), Prof S Stewart-Brown (Warwick), Prof S Singh (Warwick), Prof J Prewett (Warwick), Dr C Connor (Warwick), Dr P Patterson (Birmingham Children's Hospital NHS Foundation Trust).

Title: Understanding the epidemiology of pneumococcal carriage and disease in the era of conjugate vaccines in the United Kingdom, Finland and The Netherlands: Is the best choice PCV10 or PCV13? (Principal investigator)
Total: £5,069
Source of grant: University of Warwick Research Development Fund
Duration: 2018-2019
Other investigators: Dr T Shiri (Warwick), Prof M Keeling (Warwick).

Title: What works centre for children’s social care (Health Economics Lead and Co-Investigator)
Total: £4,846,354
Source of grant: Department for Education
Duration: 2018-2020
Lead investigator: Prof D Forrester (Cardiff)
Other investigators: Prof J Scourfield (Cardiff), Dr G Moore (Cardiff), Dr R Evans (Cardiff), Prof M Robling (Cardiff), Dr A Kemp (Cardiff).

Title: What is the effectiveness and cost effectiveness of group based parenting programmes for improving parental psychosocial health? (Health Economics Lead and Co-Investigator)
Total: £643,718
Source of grant: National Institute for Health Research Public Health Research Programme
Duration: 2018-2020
Lead investigator: Prof R Hastings (Warwick)
Other investigators: Prof G Lindsay (Warwick), Dr V Totsika (Warwick), Dr D Gillespie (Warwick), Prof K Hood (Cardiff), Dr R McNamara (Cardiff), Prof M Robling (Cardiff), Dr N Gore (Kent), Prof A Jahoda (Glasgow), Ms J Shurlock (Challenging Behaviour Foundation Early Intervention Project), Prof M Nudds (Warwick).

Title: Support package for NHS Trust-based health economics research (Principal investigator)
Total: £145,934
Source of grant: Research & Development, University Hospitals Coventry and Warwickshire
Duration: 2018-2021

Title: Induction of labour for predicted macrosomia (The 'Big Baby Trial'). (Health Economics Lead and Co-Investigator)
Total: £2,225,228
Source of grant: National Institute for Health Research Health Technology Assessment Programme
Duration: 2018-2021
Lead investigator: Prof S Quenby (Warwick)
Other investigators: Dr A Gornall (Shrewsbury and Telford Hospital NHS Trust), Dr S Deshpande (Shrewsbury and Telford Hospital NHS Trust), Prof S Gates (Warwick), Dr R Lall (Warwick), Dr J Fisher (Warwick), Prof J Gardosi (Perinatal Institute), Prof M Underwood (Warwick), Prof D Bick (Kings College London), Ms K Hillyer (Perinatal Institute), Mrs J Dewdney (Perinatal Institute).

Title: National Institute for Health Research Senior Investigator Award (Principal investigator)
Total: £360,000 (Personal Award: £15,000 per year; Research Capability Funding paid to associated NHS Trust: £75,000 per year)
Source of grant: National Institute for Health Research
Duration: 2017-2021 (01/04/2017-31/3/2021).

Title: REsearch on Children and Adults born Preterm (RECAP) (Health Economics Lead and Co-Investigator)
Total: €9,713,230 (£7,770,584)
Source of grant: European Commission Horizon 2020
Duration: 2017-2020
Lead investigator: Prof D Wolke (University of Warwick)
Other investigators: Institut National de la Santé et de la Recherche Médicale (INSERM) (France), University of Leicester (UK), Norwegian University of Science and Technology (Norway), Karolinska Institute (Sweden), University of Helsinki (Finland), Philipps Universität Marburg (Germany), University of Tartu (Estonia), University of Antwerpen (Belgium), Hvidovre Hospital (Denmark), UniversitaetsKlinikum Bonn (Germany), Instituto de Engenharia de Sistemas e Computadores, Tecnologia e Ciência (Portugal), Extensive Life (Finland), MedlawConsult (Netherlands), Concentris (Germany), European Foundation for the Care of Newborn Infants (pan-European organisation).

Title: Screening to improve health in very preterm infants in Europe (SHIPS). (Health Economics Lead and Co-Investigator)
Total: €2,993,175 (£2,217,178)
Source of grant: European Commission Horizon 2020
Duration: 2015-2019
Lead investigator: Dr J Zeitlin (INSERM, Paris)
Other investigators: University of Leicester (UK), Philipps University Marburg (Germany), Radhoud University Medical Centre (Netherlands), Department of Health of Lazio Region (Italy), University of Medical Sciences (Poland), Study Centre for Perinatal Epidemiology (Belgium), Porto Medical University (Portugal), Hvidovre University Hospital (Denmark), Karolinska Institute (Sweden), University of Tartu (Estonia), European Foundation for the Care of Newborn Infants (pan-European

organisation).

Title: Tracking the health, educational and economic impact of gestational age at birth: a longitudinal record linkage study (TIGAR) (Co-investigator)

Total: £626,817

Source of grant: Medical Research Council

Duration: 2015-2018

Lead investigator: Prof M Quigley (Oxford)

Other investigators: Prof J Kurinczuk (Oxford), Dr C Carson (Oxford), Dr O Rivero Arias (Oxford), Prof P Sammons (Oxford), Dr E Boyle (Leicester), Dr S Johnson (Leicester), Prof A Macfarlane (City), Dr N Dattani (City).

Title: UK Study of tendon Achilles Rehabilitation – multicentre randomised clinical trial (UK STAR). (Health Economics Lead and Co-Investigator)

Total: £931,261.96

Source of grant: National Institute for Health Research Health Technology Assessment Programme

Duration: 2016-2019

Lead investigator: Prof M Costa (Oxford)

Other investigators: Dr J Achten (Warwick), Dr N Parsons (Warwick), Dr Rebecca Kearney (Warwick), Mrs Malvenia Richmond (Warwick), Mr Ben Ollivere (Nottingham University Hospitals NHS Trust), Prof Sallie Lamb (Oxford).

Title: Better Outcomes for Older people with Spinal Trouble (BOOST). (Health Economics Lead and Co-Investigator)

Total: £1,999,934

Source of grant: National Institute for Health Research Programme Grants for Applied Research

Duration: 2015-2019

Lead investigator: Prof S Lamb (Oxford)

Other investigators: Dr K Barker (Oxford), Prof J Fairbank (Oxford), Prof N Arden (Oxford), Dr J Bruce (Warwick), Prof D Altman (Oxford), Prof C Hutchinson (Warwick), Prof C Mallen (Keele), Dr E Williamson (Oxford), Ms J Fitch (Nuffield Health), Dr G Collins (Oxford), Prof F Griffiths (Warwick), Dr Z Hansen (Oxford).

Title: Chronic health education and self-management study (CHESS). (Health Economics Lead and Co-Investigator)

Total: £1,999,067

Source of grant: National Institute for Health Research Programme Grants for Applied Research

Duration: 2015-2019

Lead investigator: Prof M Underwood (Warwick)

Other investigators: Dr D Ellard (Warwick), Dr G Elrington (Barts Health NHS Trust), Dr D Carnes (Queen Mary, University of London), Mrs J Hamilton-Colclough (Migraine Action), Dr K Haywood (Warwick), Dr M Matharu (UCL), Prof S Elridge (Queen Mary, University of London), Dr SW Hee (Warwick), Mrs W Thomas (The Migraine Trust), Ms M Bright (University Hospitals Coventry and Warwickshire NHS Trust), Dr H Sandhu (Warwick), Prof F Griffiths (Warwick), Prof T Pincus (Royal Holloway College), Prof S Taylor (Queen Mary, University of London).

Title: Exercise to prevent shoulder conditions in patients undergoing breast cancer treatment: The Prevention Of Shoulder Problems Study (PROSPER). (Health Economics Lead and Co-Investigator)

Total: £1,331,325

Source of grant: National Institute for Health Research Health Technology Assessment Programme

Duration: 2015-2018

Lead investigator: Dr J Bruce (Warwick)

Other investigators: Dr E Williamson (Oxford), Dr C Balmer (Warwick), Prof S Lamb (Oxford), Dr J Williams (Royal Marsden NHS Foundation Trust).

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Dr Felix Achana
Role and organisation ***Department*** ***Organisation*** ***Email***	Senior Research Fellow in Health Economics University of Warwick F.Achana@warwick.ac.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
PhD - Medical statistics	University of Leicester - 15/07/2015
MSc - Medical statistics	University of Leicester - 01/10/2010
BSc (Hons) - Nursing RN	Birmingham City University - 08/09/2004
BSc - Biology	Kwame Nkrumah University of Science and Technology - 06/10/2000

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	33 % FTE

Recent Relevant Publications

Damian R Griffin, Edward J Dickenson, Peter D H Wall, Felix Achana, Jenny L Donovan, James Griffin, Rachel Hobson, Charles E Hutchinson, Marcus Jepson, Nick R Parsons, Stavros Petrou, Alba Realpe, Joanna Smith and Nadine E Foster (2018) Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. Lancet 2018; 391: 2225–35.

Achana FA, Fleming KM, Tata LJ, Sultan AA and Petrou S (2017). Peripartum hysterectomy: an economic analysis of direct healthcare costs using routinely collected data. BJOG: An International Journal of Obstetrics and Gynaecology. p874-883.

Felix Achana, Stavros Petrou, Kamran Khan, Amadou Gaye and Neena Modi (2017. A methodological framework for assessing agreement between cost-effectiveness outcomes estimated using alternative sources of clinical and healthcare utilisation data. European Journal of Health Economics 19 (1), 75-86.

Dritsaki, Melina, Achana, Felix A., Mason, James, Petrou, Stavros. 2017. Methodological issues surrounding the use of baseline health-related quality of life data to inform trial-based economic evaluations of interventions within emergency and critical care settings: a systematic literature review. PharmacoEconomics, View

Felix Achana, Alex J Sutton, Denise Kendrick, Mike Hayes4, David R Jones, Stephanie, J Hubbard, Nicola J Cooper. A decision analytic model to investigate the cost-effectiveness of poisoning prevention practices in households with young children. BMC Public Health (2016).

Research Grants Held

None

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Associate Professor Joyce Yeung
Role and organisation ***Department*** ***Organisation*** ***Email***	Honorary Consultant in Anaesthesia and Intensive Care University Hospitals Birmingham NHS Foundation Trust j.yeung.4@warwick.ac.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
Fellow - FHEA	Higher Education Authority - 01/07/2015
Fellow - FICM	Faculty of Intensive Care Medicine - 01/10/2013
PhD -	University of Warwick - 01/11/2011
Fellow - FRCA	Royal College of Anaesthetists - 01/02/2007
MB ChB -	University of Birmingham - 31/07/2001

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	5 % FTE

Recent Relevant Publications

Patel V, Champaneria R, Dretzke J, Yeung J. Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review. BMJ open 8 (12), e020757

Couper K, Quinn T, Lall R, Devrell A, Orriss B, Seers K, Yeung J, Perkins GD. Mechanical versus manual chest compressions in the treatment of in-hospital cardiac arrest patients in a non-shockable rhythm: a randomised controlled feasibility trial. Scandinavian journal of trauma, resuscitation and emergency medicine 2018: 26 (1), 70

Poole K, Couper K, Smyth MA, Yeung J, Perkins GD. Mechanical CPR: Who? When? How? Critical Care 2018: 22 (1), 140

Yeung J, Couper K, Ryan EG, Gates S, Hart N, Perkins GD. Non-invasive ventilation as a strategy for weaning from invasive mechanical ventilation: a systematic review and Bayesian meta-analysis. Intensive care medicine 2018, 1-13

Couper K, Yeung J, Nicholson T, Quinn T, Lall R. Mechanical chest compression devices at in-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation, 2016

Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev. 2016 Feb 21;2:CD009121.

Research Grants Held

01/11/2017 £1,991,199.32 NIHR Health Technology Assessment, Co-applicant

A Randomised Controlled Trial to investigate the clinical and cost-effectiveness of Paravertebral Blockade compared with

Thoracic Epidural Blockade in reducing Chronic Post-Thoracotomy Pain (TOPIC2)

01/03/2016 £128030 Resuscitation Council UK, Co-applicant

Effect of hospital resuscitation service provision on survival from in-hospital cardiac arrest

01/03/2016 £ 15241.05 Resuscitation Council UK, Chief Investigator

The School Lifesavers Study – A randomised controlled trial comparing the impact of Lifesaver Programme only, Lifesaver with face-to-face training and face-to-face training only on CPR knowledge, skills and attitudes in school children

01/01/2015 £470720.00 NIHR Post-Doctoral Fellowship - Four years, Chief Investigator

In elderly patients undergoing fractured neck of femur fixation, does the use of regional anaesthesia compared to general anaesthesia reduce incidence of post-operative delirium (GeRAFFE)? A programme of research

01/02/2015 £ 22435.00 Resuscitation Council UK, Chief Investigator
Evaluation of instructor-led debriefing in Advanced Life Support course (ATEAM-II)

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Professor Gavin D Perkins
Role and organisation	Director of Warwick CTU and Professor of Critical Care Medicine
Department	Warwick Medical School and University Hospitals Birmingham
Organisation	University of Warwick
Email	g.d.perkins@warwick.ac.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
Fellow - Intensive Care Medicine	Faculty of Intensive Care Medicine - 01/07/2011
Fellow - Medicine	Royal College of Physicians (London) - 01/06/2011
MD - Medicine	University of Birmingham - 01/08/2008
Fellow - Immediate Medical Care	Royal College of Surgeons (Edinburgh) - 01/09/2001
MB ChB - Medicine	University of Birmingham - 01/08/1995

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	10 % FTE

Recent Relevant Publications

A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest.

Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M, Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R; PARAMEDIC2 Collaborators.

N Engl J Med. 2018 Aug 23;379(8):711-721. doi: 10.1056/NEJMoa1806842. Epub 2018 Jul 18.

Effect of Protocolized Weaning With Early Extubation to Noninvasive Ventilation vs Invasive Weaning on Time to Liberation From Mechanical Ventilation Among Patients With Respiratory Failure: The Breathe Randomized Clinical Trial.

Perkins GD, Mistry D, Gates S, Gao F, Snelson C, Hart N, Camporota L, Varley J, Carle C, Paramasivam E, Hoddell B, McAuley DF, Walsh TS, Blackwood B, Rose L, Lamb SE, Petrou S, Young D, Lall R; Breathe Collaborators.

JAMA. 2018 Nov 13;320(18):1881-1888.

Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial.

Perkins GD, Lall R, Quinn T, Deakin C, Cooke MW, Horton H, Lamb SE, Slowther AM, Woollard M, Carson A, Smyth M, Whitfield R, Williams A, Pocock H, Black JJM, Wright J, Han K, Gates S.

Lancet 2015 385(9972):947-55

Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis.

Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, Mason AJ, Cross M, Al-Beidh F, Best-Lane J, Brealey D, Nutt CL, McNamee JJ, Reschreiter H, Breen A, Liu KD, Ashby D.

N Engl J Med. 2016 Oct 27;375(17):1638-1648

Simvastatin in the acute respiratory distress syndrome.

McAuley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, Johnston P, Hopkins PA, Johnston AJ, McDowell C, McNally C; HARP-2 Investigators; Irish Critical Care Trials Group.

N Engl J Med. 2014 Oct 30;371(18):1695-703

Improving the efficiency of advanced life support training: a randomized, controlled trial.

Perkins GD, Kimani PK, Bullock I, Clutton-Brock T, Davies RP, Gale M, Lam J, Lockey A, Stallard N; Electronic Advanced Life Support Collaborators.

Ann Intern Med. 2012 Jul 3;157(1):19-28.

Research Grants Held

Out-of-Hospital Cardiac Arrest Outcomes (OHCAO) Registry; Resuscitation Council (UK) £226,076 and British Heart Foundation £799,665

Evaluation of Emergency Care Treatment Plans (RESPECT); NIHR HS&DR (15/15/09), £795,327.36

Epidemiology and Outcome of Out-of-Hospital Cardiac Arrest; Resuscitation Council (UK) £137,231 and British Heart Foundation £151,500.

Gatekeeping in Intensive Care – Understanding and Improving the Decision-Making Process Surrounding Admission to the Intensive Care Unit; NIHR HS&DR (13/10/14), £703,118.00

Randomised placebo controlled trial of adrenaline for out-of-hospital cardiac arrest; HTA (12/127/126), £2,751,276

An Efficacy and Mechanism Evaluation Study of Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis; MRC-NIHR £1,085,171

Study into the Reversal of septic shock with beta blocakade (STRESS-BB); NIHR EME (14/150/85), £1,582,982

Centre of Research Excellence Pre-Hospital Emergency Care (CRE PEC); NHMRC (1116453), AUS$2,499,626

A multi-centre study of the mind, brain, consciousness and near death experiences during cardiac arrest; John Templeton Foundation, US$1,820,606

Protective ventilation with veno-venous lung assist in respiratory failure, The REST Trial; HTA (13/143/02), £2,113,673

Reduction of oxygen after cardiac arrest: The EXACT trial; NHMRC (1107509), AUS$£1,891,021

Multi-centre randomised controlled trial of pre-hospital blood product administration versus standard care for traumatic haemorrhage; NIHR EME (14/152/14); £1,719,468

Do not attempt cardiopulmonary resuscitation (DNACPR) decisions; HS&DR, £181,646

Protocolised trial of invasive and non-invasive weaning off ventilation; HTA, £1,278,762

Systematic review and cost-effectiveness analysis of pre-hospital non-invasive ventilation for acute respiratory failure; HTA, £136,297

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Dr Ranjit Lall
Role and organisation	Principal Research Fellow Statistician
Department	Warwick Medical School, University of Warwick
Organisation	University of Warwick
Email	r.lall@warwick.ac.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
PhD - The application of Ordinal Regression Models in Quality of Life Scales used in Gerontology	University of Sheffield - 01/02/2004

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	10 % FTE

Recent Relevant Publications

1. Perkins, Gavin D., Ji, Chen, Deakin, Charles D., Quinn, Tom, Nolan, Jerry P., Scomparin, Charlotte, Regan, Scott, Long, John, Slowther, Anne, Pocock, Helen, Lall Ranjit et al. (2018) A randomized trial of epinephrine in out-of-hospital cardiac arrest. New England Journal Of Medicine . doi:10.1056/NEJMoa1806842

2. Lamb, Sally, Sheehan, Bart, Atherton, Nicky, Nichols, Vivien, Collins, Helen, Mistry, Dipesh, Dosanjh, Sukhdeep, Slowther, Anne Marie, Khan, Iftekhar, Petrou, Stavros and Lall, Ranjit (2018) Dementia and physical activity (DAPA) trial of moderate to high intensity exercise training for people with dementia : randomised controlled trial. BMJ, 361 . k1675. doi:10.1136/bmj.k1675

3. Keene, David J., Lamb, S. E. (Sallie E.), Mistry, Dipesh, Tutton, Elizabeth, Lall, Ranjit, Handley, Robert and Willett, Keith (2018) Three-year follow-up of a trial of close contact casting vs surgery for initial treatment of unstable ankle fractures in older adults. JAMA: The Journal of the American Medical Association, 319 (12). pp. 1274-1276. doi:10.1001/jama.2018.0811

4. Ji C., Quinn T., Gavalova L., Lall R,, Scomparin C., Horton J., Deakin C., Pocock H., Smyth M., Rees N., Brace-McDonnell S., Gates S. and Perkins G. Is data linkage feasible for cardiac arrest research? Lessons from the PARAMEDIC Trial: a cluster randomised trial of mechanical chest compression in out of hospital cardiac arrest. BMJ Open 2018

5. Marti J, Hulme C, Ferreira Z, Nikolova S, Lall R, Kaye C, Smyth M, Kelly C, Quinn T, Gates S, Deakin CD, Perkins GD. The cost-effectiveness of a mechanical compression device in out of hospital cardiac arrest (Paramedic I Trial). Resuscitation 2017: Vol 117: pp.1-7 (IF: 5.230)

6. Willett, Keith, Keene, David J., Mistry, Dipesh, Nam, Julian, Tutton, Elizabeth, Handley, Robert, Morgan, Lesley, Roberts, Emma, Briggs, Andrew, Lall, Ranjit, Chesser, Timothy J. S., Pallister, Ian and Lamb, Sallie E. (2016) Close contact casting vs surgery for initial treatment of unstable ankle fractures in older adults. JAMA: The Journal of the American Medical Association, 316 (14). 1455. doi:10.1001/jama.2016.14719

Research Grants Held

1. STRESS-L STudy into the REversal of Septic Shock with Beta Blockade (NIHR EME). Clinical Lead Applicant:

T. Whitehouse, CTU Lead Applicant: R LALL (2017-2021) £1, 600, 000

2. BIG BABY Trial Induction of labour for predicted macrosomia (NIHR HTA). Lead Applicant: S. Quenby,

Co-applicant: R LALL (2018-2021) £2,280,000

3. ADAPT – SEPSIS Trial Biomarker-guided duration of antibiotic treatment (NIHR HTA). Lead Applicant: P. Dark, Co-applicant: R LALL (2017-2022) £1, 600, 000

4. I-WOTCH 14/224/04). Improving the Wellbeing of people with Opioid Treated Chronic pain comparing a multi-component self-management intervention v. usual care. Lead Applicant: M.

Underwood, Co-applicant: R LALL (2016-2020) £1, 578, 213.

5. 13/84/10: PROSPER. Exercise to prevent shoulder conditions in patients undergoing breast cancer treatment. The PRevention Of Shoulder Problems Study. Lead Applicant: J. Bruce; Co-applicant: R LALL (2105-2019), £1328, 447

6. 12/127/126: PARAMEDIC 2.Randomised placebo controlled trial of adrenaline for out of hospital cardiac arrest. Lead Applicant: G. Perkins; Co-applicant: R LALL (2014-2019) £2, 751, 277

7. 10/134/06: BREATHE. Protocolised trial of invasive and non-invasive weaning off ventilation. Lead Applicant: G. Perkins; Co-applicant: R LALL (2013-2018) £1, 278, 762

8. 09/80/04: DAPA- Dementia And Physical Activity: Physical activity intervention for community dwelling people with mild to moderate dementia. Lead Applicant: S E Lamb; Joint Co-applicant: R LALL (2011-2016) £1, 703, 705

9. 08/14/41. PREFIT: Prevention of Falls Injury Trial. Lead Applicant: S E Lamb; Lead Statistician: R LALL (2010-2019) £2, 676, 197

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Dr Alison Walker
Role and organisation	Medical Director
Department	Clinical Directorate
Organisation	West Midlands Ambulance Service NHS Foundation Trust
Email	alison.walker@hdft.nhs.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
Other - Sports and Exercise Medicine, MFSEM	RCS Edinburgh - 01/07/2018
Fellow - Immediate Medical Care	Royal College of Surgeons of Edinburgh - 31/03/2007
Other - Postgraduate Certificate in Health Research	Univeristy of Leeds - 31/07/2002
Fellow - Emergency Medicine	College of Emergency Medicine - 30/04/2002
Fellow - General Surgery	Royal College of Surgeon of England - 28/02/1998
MB ChB - Medicine	University of Cambridge - 13/08/1995
BMed Sci - Medical Sciences	University of Cambridge - 27/06/1992
Fellow - Dental Surgery	Royal College of Surgeons of England - 22/12/1991
Other - Batchelor of Dental Surgery	Edinburgh Univeristy - 30/06/1987

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	5 % FTE

Recent Relevant Publications

Prospective study of injury severity scores during a season of British Superbike racing
DP O'Dowd, S Robertshaw, A Walker, DG Roberts, H Romer
Trauma: October 2013 15(4) 265-70

A mannequin study comparing suitability of the i-gel with a laryngeal mask airway device
J Mark, A Walker, C Davey
Journal of Paramedic Practice, March 2011; 3: 8

"At the sharp end": does ambulance dispatch data from south Yorkshire support the picture of increased weapon-related violence in the UK?
J T Gray, A Walker
Emergency Medicine Journal 2009;26:741-742

Is referral to emergency care practitioners by general practitioners in-hours effective?
J T Gray, A Walker
Emergency Medicine Journal 2009;26:611-612

Mobile radiography at a music festival
A Walker, J Brenchley, N Hughes
Emergency Med J 2009;26:613

AMPDS categories: are they an appropriate method to select cases for extended role ambulance practitioners?
J T Gray, and A Walker
Emergency Medicine Journal, Sep 2008; 25: 601 - 603.

Research Grants Held

N/A

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Dr Gordon Fuller
Role and organisation	NIHR Clinical Lecturer
Department	School of Health and Related Research
Organisation	The University of Sheffield
Email	g.fuller@sheffield.ac.uk

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
PhD - Epidemiology and Health Economics	University of Sheffield - 17/08/2015
Other - MPH - Masters of Public Health	University of Glasgow - 18/10/2012
Other - MRCS - Membership of Royal College of Surgeons	Royal College of Surgeons of England - 12/02/2008
MB ChB - Clinical Medicine	University of Glasgow - 16/07/2002
BSc (Hons) - Pharmacology	University of Glasgow - 14/07/1999

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	2 % FTE

Recent Relevant Publications

• Fuller GW, Goodacre S, Keating S, Perkins G, Ward M, Rosser A, Gunson I, Miller J, Bradburn M, Thokala P, Harris T, Carson A, Marsh M & Cooper C (2018) The ACUTE (Ambulance CPAP: Use, Treatment effect and economics) feasibility study: a pilot randomised controlled trial of prehospital CPAP for acute respiratory failure. Pilot and Feasibility Studies, 4(1).

• Lecky F, Russell W, Fuller G, McClelland G, Pennington E, Goodacre S, Han K, Curran A, Holliman D, Freeman J, Chapman N, Stevenson M, Byers S, Mason S, Potter H, Coats T, Mackway-Jones K, Peters M, Shewan J & Strong M (2016) The Head Injury Transportation Straight to Neurosurgery (HITS-NS) randomised trial: a feasibility study. Health Technology Assessment, 20(1), 1-198.

• Fuller G, McClelland G, Lawrence T, Russell W & Lecky F (2016) The diagnostic accuracy of the HITSNS prehospital triage rule for identifying patients with significant traumatic brain injury: A cohort study. European Journal of Emergency Medicine, 23(1), 61-64.

Research Grants Held

• NIHR HTA. MATTS: Major Trauma Triage Study. Chief Investigator. £900,000

• NIHR HTA. ACUTE: Ambulance CPAP: Use, Treatment effect and Economics randomised controlled trial. Chief investigator. £600,000

• NIHR HTA. TIME: Take home naloxone Intervention Multicentre Emergency setting feasibility trial. Co-investigator. £563,734

CO-APPLICANT INFORMATION

Co-applicant Information

Name	Dr Julian Mark
Role and organisation	
Department	
Organisation	Yorkshire Ambulance Service NHS Trust
Email	j.mark@nhs.net

Co-applicant Information – Qualifications

Degree/subject professional Qualification	Awarding body, date of award
Fellow - Medical Leadership and Management	Faculty of Medical Leadership and Management - 01/08/2017
Certificate - Medical Law	Northumbria University - 01/08/2012
Diploma - Immediate Medical Care	Faculty of Pre-Hospital Care, Royal College of Surgeons Edinburgh - 01/08/2010
MB ChB - Medicine	University of Leeds - 01/08/1994
BSc (Hons) - Chemical Pathology	University of Leeds - 01/08/1991

Patient/Service user or carer applicants

Patient / service users or carer applicants information

RECENT PUBLICATIONS AND RESEARCH GRANTS

Commitment to this Research Project	5 % FTE

Recent Relevant Publications
Brown TP, Booth S, Hawkes CA, Soar J, Mark J, Mapstone J, Fothergill RT, Black S, Pocock H, Bichmann A, Gunson I, Perkins GD. Characteristics of neighbourhoods with high incidence of out-of-hospital cardiac arrest and low bystander cardiopulmonary resuscitation rates in England. Eur Heart J Qual Care Clin Outcomes. 2019 Jan 1;5(1):51-62. doi: 10.1093/ehjqcco/qcy026.

Research Grants Held