WARWICK
CLINICAL TRIALS UNIT

11th March 2021

Dear West of Scotland Research Ethics Committee,

Study title: Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma: PACKMaN
IRAS Project ID: 266748 / 1003404
REC Ref: 20/WS/0126
Amendment Ref: Substantial Amendment 02

Please find attached the following amended documents for review for the above-mentioned trial. A summary of the changes are provided overleaf.

Document	Version	Date
Substantial Amendment Tool	N/A	24/02/2021
Protocol	3.0	09/03/2021
Brief PIL for Paramedics	2.0	09/03/2021
Patient Information Sheet	3.0	24/02/2021
Consent form (Patient)	2.0	24/02/2021
Consent form (Legal representative)	2.0	24/02/2021
Cover letter (Patient)	2.0	24/02/2021
Reminder cover letter (Patient)	2.0	24/02/2021
Cover letter (Legal representative)	2.0	24/02/2021
Reminder cover letter (Legal representative)	2.0	24/02/2021
Cover email and SMS (Patient)	1.0	24/02/2021
Cover email and SMS (Legal representative)	1.0	24/02/2021
E-consent form (Patient)	2.0	24/02/2021
E-consent form (Legal representative)	2.0	24/02/2021
ED leaflet	2.0	09/03/2021

Please do not hesitate to contact us should you require any further information.

Kind regards,

Charlotte Scomparin
Trial Manager

Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Campus
Coventry, CV4 7AL
Tel: 02476 150478
Email: packman@warwick.ac.uk

Document	Key changes
Protocol	- Updated details on the title page - Added CI and statistician signatures - Sponsor contact name updated - Updated the name of the Trial Manager - Removed personal details of co-applicants - Added details of the TSC and DMC - Trial Summary – added the word 'randomised' to trial design - Added abbreviations to the glossary - Updated typos and formatting throughout - 2.1 – corrected typo on age range of 16 and over - Figure 2 removed reference to n= as this is not required in this diagram - Figure 3 updated wording to remove mention of a paramedic using the next sequential IMP box. The justification for this is that it will not be practical crews to find the next sequentially numbered box when signing out drug packs. Participants will also not be recruited by sequential pack numbers so this is unnecessary. - Figure 4 updated with new consent process (see 2.8) - 2.2 – added new table at the request of the funder to outline decision for moving from the pilot phase to main recruitment phase of the trial - 2.2 – deviations and violations changed to 'non-compliances' - 2.4 – updated the vital signs of secondary outcomes as the previous list was an error - 2.4 – updated the incidence of side effects and adverse events as the previous 'other' list was an error - Renumbered section 2 from 2.6 due to error in previous formatting - 2.6 clarification that the paramedic will advise the research team when a patient has been recruited - 2.7 – removed reference to attending paramedic taking consent - 2.8 – added reference to figure 3 and 4 to the consent process title - 2.8 – updated consent process to remove full written informed consent being taken by attending paramedic. The justification for this is that, for written informed consent to be taken in the ambulance it requires that the patient is deemed to have capacity, their pain is under control, there is no need for ongoing clinical care that would interrupt the consent process, and there is sufficient time for the patient to consider their participation and sign the consent form before arriving at hospital. In reality, we believe this will be a very rare occurrence and that patients' capacity to provide written informed consent at this stage will be impaired due to ongoing pain and/or side effects of ketamine or morphine. Instead, full written informed consent will be taken by the Research Paramedic as soon as practically possible after the patient has arrived at hospital. This change has the support of our ambulance service partners.

Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Campus
Coventry, CV4 7AL
Tel: 02476 150478
Email: packman@warwick.ac.uk

	- 2.8 Option for remote consent included, as in many cases it will not be possible to conduct a face-to-face visit. - 2.10.4 – clarified the dose for paracetamol - 2.11.1 – added programming to the list of people unblinded. This is to enable them to provide the emergency unblinding process - 2.11.2 – updated the wording for emergency unblinding to make the process clearer. Additional text added describing backup process - 2.11.3 – added the ability for legal representatives to be able to request unblinding information. Clarified that unblinding after trial completion will only be carried out with CI oversight and approval - 3.1 updated the schedule of delivery and data collection to better reflect the trial and correct error in when the global impression of change will be collected. Pre-hospital informed consent removed - 3.2.2 side effects removed from list of hospital data collection as this data will be captured from ambulance service medical records and via SAE reports - 3.2.3 Removed details of consent process as this is already described in 2.8. Option for telephone questionnaire reminder added. - 4.2 – amended to make clearer - 4.2.1 – rearranged and clarified some wording to make what needs reporting clearer - 4.7 – added text to explain that a substantial amendment would be submitted within 2 weeks of notifying the REC and MHRA of urgent safety measures - 5.1 – removed mention of the fact that CTU will receive personal identifiable data as they will not - 5.4 Removed reference to patient identifiable data being stored at WCTU - 6.2.3.3 – corrected error on age range to include 60 year olds - 6.2.3.3 – changed injury severity score to injury severity as demonstrated by a patient record on TARN. A patient being added to TARN gives an indication of the severity of their injury. - 6.2.3.3 - Gender updated at the request of the ambulance services - 6.5 removed reference to EQ-5D at hospital discharge as this was left in the protocol in error - 7.2 – removal of CAG approval as the trial does not require CAG - 7.2 – added reference to ISRCTN and EudraCT registries for publications - 8 – now included as part of section 7.
Brief PIL for Paramedics	Some updates to text to make it clearer what medication would be given as part of the trial, and what would be given as standard treatment
Cover letter (patient)	Removed option for contact via email as the consent conversation needs to be a two-way real-time conversation
Reminder cover letter (patient)	Removed option for contact via email as the consent conversation needs to be a two-way real-time conversation

Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Campus
Coventry, CV4 7AL
Tel: 02476 150478
Email: packman@warwick.ac.uk

Cover letter (LR)	Removed option for contact via email as the consent conversation needs to be a two-way real-time conversation Removed place of death as we do not require this data
Reminder cover letter (LR)	Removed option for contact via email as the consent conversation needs to be a two-way real-time conversation Removed place of death as we do not require this data
Cover email and SMS (patient)	New document to use when the Patient Information Sheet is sent electronically to the patient
Cover email and SMS (LR)	New document to use when the Patient Information Sheet is sent electronically to the patient
Consent form (LR)	Point 1 edited to include version number and date of Patient Information Sheet provided Space for independent witness signature added
Consent form (participant)	Space for independent witness signature added TNO number removed as this will be the same as study number
E-consent form design (patient)	New document to show the design of the e-consent form on Qualtrics – this includes four fields hidden to the user (Name of person receiving consent, Date, Countersignature (if witnessed), Date) as the Research Paramedic will update these fields once the patient has signed and submitted the e-consent form. The version number of the e-consent form matches the paper form.
E-consent form design (LR)	New document to show the design of the e-consent form on Qualtrics – this includes four fields hidden to the user (Name of person receiving consent, Date, Countersignature (if witnessed), Date) as the Research Paramedic will update these fields once the patient has signed and submitted the e-consent form. The version number of the e-consent form matches the paper form.
PIL	Centre number and trial number removed Typo corrections Added sentence to explain that consent form may be signed electronically Remove reference to completing questionnaires by email Updated data transparency section to make this clearer Link to University of Warwick privacy notice added Details of DPO added Named Chief Investigator updated Details of REC approval added
ED leaflet	Updated to include contact details for emergency unblinding and SAE reporting
Other amendments	**New sites added:** University Hospitals Coventry & Warwickshire NHS Trust George Eliot Hospital NHS Trust Warwick Hospital (South Warwickshire NHS Foundation Trust)

Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Campus
Coventry, CV4 7AL
Tel: 02476 150478
Email: packman@warwick.ac.uk

	Good Hope Hospital (University Hospitals Birmingham NHS Foundation Trust) Queen Elizabeth Hospital (University Hospitals Birmingham NHS Foundation Trust) Heartlands Hospital (University Hospitals Birmingham NHS Foundation Trust) Solihull Hospital (University Hospitals Birmingham NHS Foundation Trust) Walsall Manor (Walsall Healthcare NHS Trust) Sandwell General Hospital (Sandwell and West Birmingham NHS Trust) Birmingham City Hospital (Sandwell and West Birmingham NHS Trust) Russell's Hall Hospital (The Dudley Group NHS Foundation Trust) Royal Stoke University Hospital (University Hospitals of North Midlands NHS Trust) County Hospital Stafford (University Hospitals of North Midlands NHS Trust) Queens Hospital Burton (University Hospitals of Derby and Burton NHS Foundation Trust) Royal Derby Hospital (University Hospitals of Derby and Burton NHS Foundation Trust) Alexandra Hospital (Worcestershire Acute Hospitals NHS Trust) Worcestershire Royal Hospital (Worcestershire Acute Hospitals NHS Trust) New Cross Hospital (Royal Wolverhampton NHS Trust) Macclesfield District Hospital (East Cheshire NHS Trust) Hereford County Hospital (Wye Valley NHS Trust) Princess Royal Hospital (The Shrewsbury and Telford Hospital NHS Trust) Royal Shrewsbury Hospital (The Shrewsbury and Telford Hospital NHS Trust) Birmingham Children's Hospital (Birmingham Women's and Children's NHS Foundation Trust) Leicester Royal Infirmary (University Hospitals of Leicester NHS Trust) John Radcliffe Hospital (Oxford University Hospitals NHS Foundation Trust) Horton General Hospital (Oxford University Hospitals NHS Foundation Trust) Leeds General Infirmary (The Leeds Teaching Hospitals NHS Trust) James Cook University Hospital (South Tees Hospitals NHS Foundation Trust) Hull Royal Infirmary (Hull University Teaching Hospitals NHS Trust) Northern General Hospital (Sheffield Teaching Hospitals NHS Foundation Trust) Pinderfields Hospital (The Mid Yorkshire Hospitals NHS Trust) Harrogate District Hospital (Harrogate and District NHS Foundation Trust) Bradford Royal Infirmary (Bradford Teaching Hospitals NHS Foundation Trust) Scarborough General Hospital (York Teaching Hospital NHS Foundation Trust) Airedale General Hospital (Airedale NHS Foundation Trust) Huddersfield Royal Infirmary (Calderdale and Huddersfield NHS Foundation Trust) Doncaster Royal Infirmary (Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust) Barnsley Hospital (Barnsley Hospital NHS Foundation Trust) Rotherham General Hospital (Rotherham NHS Foundation Trust) Darlington Memorial Hospital (County Durham and Darlington NHS Foundation Trust)

Warwick Clinical Trials Unit
University of Warwick
Gibbet Hill Campus
Coventry, CV4 7AL
Tel: 02476 150478
Email: packman@warwick.ac.uk