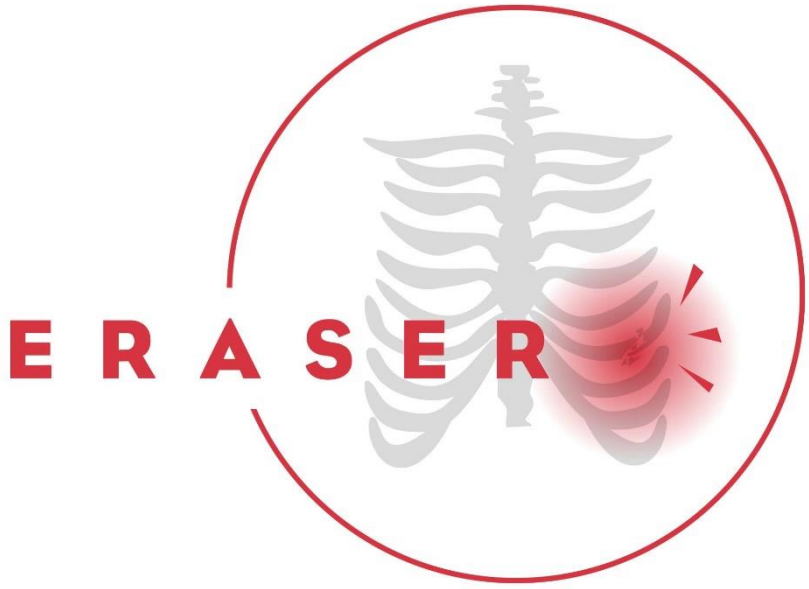
ERASER TRIAL PROTOCOL



Early **R**ib **A**nalgesia with **SER**ratus: **ERASER** Trial

A Pragmatic Randomised Control Trial Evaluating the Clinical and Cost-Effectiveness of Serratus Anterior Plane Block with Catheter Insertion compared to Usual Care in Patients with Multiple Rib Fractures

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number:	**1.0**
Version Date:	**20th July 2022**

Protocol Development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

Funding and Support in Kind	
Funder	Financial and non-financial support given:
National Institute for Health Research (NIHR)	£1,782,916.15
Funding Scheme	Funder's reference number
NIHR Health Technology Assessment (HTA) Programme	NIHR130632
Funding Call	
19/59 HTA Researcher-led call Primary Research	
This study is funded by the NIHR HTA programme as referenced above. The funder had no role in the trial design. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funder will have no role in the data collection, trial management, data analysis or interpretation of data, or in the writing of the final report.	

Chief Investigator (CI) Signature Page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

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

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

Trial Name:	ERASER Trial
Protocol Version Number:	Version: __ __
Protocol Version Date:	__ __ / __ __ __ / __ __ __ __
Chief Investigator Name:	Prof Tonny Veenith
Signature and date:	_____ __ __ / __ __ __ / __ __ __ __

Sponsor statement:

By signing the IRAS form for this trial, the University of Birmingham, acting as the sponsor of this trial confirms approval of this protocol.

Compliance statement:

This protocol describes the ERASER Trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the ERASER Trial.

The trial will be conducted in compliance with the approved protocol, the Principles of Good Clinical Practice (GCP) as defined by the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Mental Capacity Act 2005. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) Signature Page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

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

Trial Name: Protocol Version Number:	ERASER Trial Version: __ __
Protocol Version Date:	__ __ / __ __ __ / __ __ __ __
Principal Investigator Name:	
Name of Site:	
Signature and Date:	_____ __ __ / __ __ __ / __ __ __ __

Once signed, please forward a copy to the ERASER Trial Office.

Administrative Information

Reference Numbers	
Sponsor number:	RG_20-064
ISRCTN reference number:	TBC
IRAS reference number:	307628

Trial Office Contact Details	
Birmingham Clinical Trials Unit (BCTU) Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham Birmingham B15 2TT	Tel: 0121 415 8445 / 0121 414 7943 Email: ERASER@trials.bham.ac.uk
Randomisation website	https://bctu-redcap.bham.ac.uk
Trial website	www.birmingham.ac.uk/ERASER
Trial social media	@EraserTrial

Chief Investigator	
Professor Tonny Veenith	Consultant in Neurocritical care and Critical Care Medicine Deputy Director, Trauma Science Macintosh Chair
Institute of Inflammation and Ageing College of Medical and Dental Sciences University of Birmingham Birmingham B15 2TT	Tel: 0741 523 6319 Email: t.v.veenith@bham.ac.uk

Sponsor	
University of Birmingham	Dr Birgit Whitman Head of Research Governance and Integrity
Room 106, Research Governance Support Aston Webb Building University of Birmingham B15 2TT	Email: researchgovernance@contacts.bham.ac.uk

Trial Management Group	
Chief Investigator	
Prof Tonny Veenith	Consultant in Neurocritical Care and Critical Care Medicine, University of Birmingham
Co-Chief Investigator	
Prof Fang Gao Smith	Professor in Anaesthesia, Critical Care and Pain, University of Birmingham
Co-Investigators	
Dr Tony Whitehouse	Consultant and Reader in Critical Care and Anaesthesia, University Hospitals Birmingham NHS Foundation Trust
Dr Carl Hillerman	Consultant in Anaesthesia, University Hospitals Coventry and Warwickshire NHS Trust
Dr Babu Naidu	Consultant in Thoracic Surgery, University Hospitals Birmingham NHS Foundation Trust
Dr Laura Beard	Research Training Fellow, University Hospitals Birmingham NHS Foundation Trust
Mr Ansar Mahmood	Consultant Orthopaedic Surgeon, University Hospitals Birmingham NHS Foundation Trust
Dr David McWilliams	Consultant Physiotherapist, University Hospitals Birmingham NHS Foundation Trust
Ms Carla Jarrett	Patient and Public Involvement Representative
Ms Aprella Fitch	Patient and Public Involvement Representative
Ms Laura Nice	Patient and Public Involvement Lead, University Hospitals Birmingham NHS Foundation Trust
Dr Raymond Oppong	Senior Lecturer in Health Economics, University of Birmingham
Miss Gemma Slinn	Trials Management Team Leader, Birmingham Clinical Trials Unit, University of Birmingham
Mr Rajnikant Mehta	Senior Medical Statistician, Birmingham Clinical Trials Unit, University of Birmingham
Dr Fiona Howroyd	Physiotherapist and Research Fellow, University of Birmingham
Dr Rajneesh Sachdeva	Consultant Anaesthetist, Research Fellow, University of Birmingham
Dr Errin Lawrence	Research Fellow, University of Birmingham
ERASER Trial Office	
Dr Naveed Saeed	Trial Manager, Birmingham Clinical Trials Unit, University of Birmingham
Ms Alisha Maher	Statistician, Birmingham Clinical Trials Unit, University of Birmingham

Trial Steering Committee	
Chair:	
Andrew Klein	Cardiothoracic Anaesthetist, Royal Papworth Hospital NHS Foundation Trust
Independent Members:	
Prof. Catherine Hewitt	Professor of Trials and Statistics and Deputy Director of York Trials Unit, University of York
On behalf of the Trial Management Group:	
Prof. Tonny Veenith	Consultant in Neurocritical Care and Critical Care Medicine, University of Birmingham
Prof. Fang Gao Smith	Professor in Anaesthesia, Critical Care and Pain, University of Birmingham

Data Monitoring Committee	
Chair:	
Independent Members:	
Prof. Graeme MacLennan	Professor of Medical Statistics and the Director of the Centre for Health Care Randomised Trials (CHaRT), University of Aberdeen

Trial Summary

Title	The ERASER Trial: Early Rib Analgesia with Serratus. A pragmatic randomised control trial evaluating the clinical and cost-effectiveness of serratus anterior plane block with catheter insertion compared to usual care in patients with multiple rib fractures.
Acronym	ERASER

Objectives	<u>Primary objective</u>
	
	To determine whether treating multiple rib fractures (MRF) patients with serratus anterior plane block (SAP) decreases the rates of pneumonia five days after randomisation, as defined by a blinded end point review committee, the clinical pulmonary infection score (CPIS) and all available trial related clinical information.
	
	<u>Secondary objectives</u>
	
	To determine whether treating patients with MRF with SAP:
	
	• Reduces pain – this will be assessed through a numerical rating scale of 0-10, recorded every 4 hours, day 1 to 5, day 14 and before discharge, and by the patient-reported Brief Pain Index (BPI) at one and three months post-randomisation.
	• Improves ventilatory function - measured by incentive spirometry, peak expiratory flow twice a day via the daily assessment log until discharge
	• Reduces the number of days ventilated and the requirement for invasive/non-invasive methods
	• Improves 30-day mortality and 3-month mortality
	• Impacts opiate consumption such as morphine and related compounds
	• Reduces hospital re-admission within 30 days of discharge
	• Is cost-effective in the NHS setting assessed through a cost-utility analysis
	• Impacts Patient-Reported Outcome Measures (PROMs) at one and three months post-randomisation:
	  ○ EQ-5D-5L
	  ○ Medical Research Council (MRC) dyspnoea scale (at 3 months only)
	  ○ BPI
	  ○ McGill Pain Questionnaire (SF-MPQ-2)

Trial Design	A pragmatic, multicentre, open-label, 1:1 two-arm allocation concealed randomised controlled trial with an internal pilot and complete economic evaluation.
Target Population	Patients aged ≥16 years with unilateral or bilateral ≥3 MRF following blunt chest trauma that occurred ≤72 hours before hospital admission.
Eligibility Criteria	<u>Inclusion criteria</u> • Patients ≥16 years with unilateral or bilateral ≥3 rib fractures following blunt chest trauma • Traumatic injury that occurred ≤72 hours before hospital admission. <u>Exclusion criteria</u> • Severe traumatic brain injury with a predicted ventilatory requirement >7 days • Acute quadriparesis • Spinal fracture precluding mobilisation • Penetrating trauma or open rib fractures • Upper airway injury requiring intubation and mechanical ventilation with an expected dependency of more than 5 days (e.g., tracheal disruption) • Any chest wall injuries that preclude a catheter insertion

	• Not anticipated to survive ≥48 hours • Contamination or infection at the site of potential SAP insertion • Any contraindication for the SAP block catheter insertion • Patients of childbearing age who have tested positive for pregnancy
Sample Size	824 participants
Setting	Intensive Care Units and wards within NHS Major Trauma Centres in the United Kingdom with a track record of participating in critical care research and confirmed to have access to MRF patient populations.
Intervention arm Control Arm	SAP + usual care SAP catheter inserted, under ultrasound guidance, in the lateral chest wall between latissimus dorsi and serratus anterior muscles in the midaxillary line. A local anaesthetic will be infused using a continuous infusion pump, according to local standard practice. Usual care Usual NHS trauma care, which may consist of twice a day physiotherapy, multimodal analgesia, incentive spirometry when possible and rib fixation.

Outcome Measures	Primary outcome
	
	1. New diagnosis of pneumonia, as agreed by a blinded end point assessment committee[1], five days after randomisation.
	
	Secondary outcomes
	
	1. Pain assessed using a numerical rating scale (0-10), recorded every 4 hours, day 1 to 5, day 14 and before discharge, and by the patient-reported BPI at one and three-months post-randomisation.
	2. Ventilatory function measured by incentive spirometry and peak expiratory flow twice a day via the daily assessment log until discharge
	3. Number of days ventilated and the requirement for invasive/non-invasive methods
	4. 30 day and 3 month mortality
	5. Complications and safety data associated with SAP
	6. Opiate consumption such as morphine and related compounds
	7. Length of stay in hospital and critical care level two/three facility
	8. Hospital re-admission within 30 days of discharge
	9. Patient-Reported Outcome Measures (PROMs) at 1 and 3 months:
	  ○ EQ-5D-5L
	  ○ Medical Research Council (MRC) dyspnoea scale at 3 months only
	  ○ Brief Pain Index (BPI)
	  ○ McGill Pain Questionnaire (SF-MPQ-2)

[1] The blinded end point review committee will make their diagnosis based CPIS and all available trial realted clinical information

Trial Schema

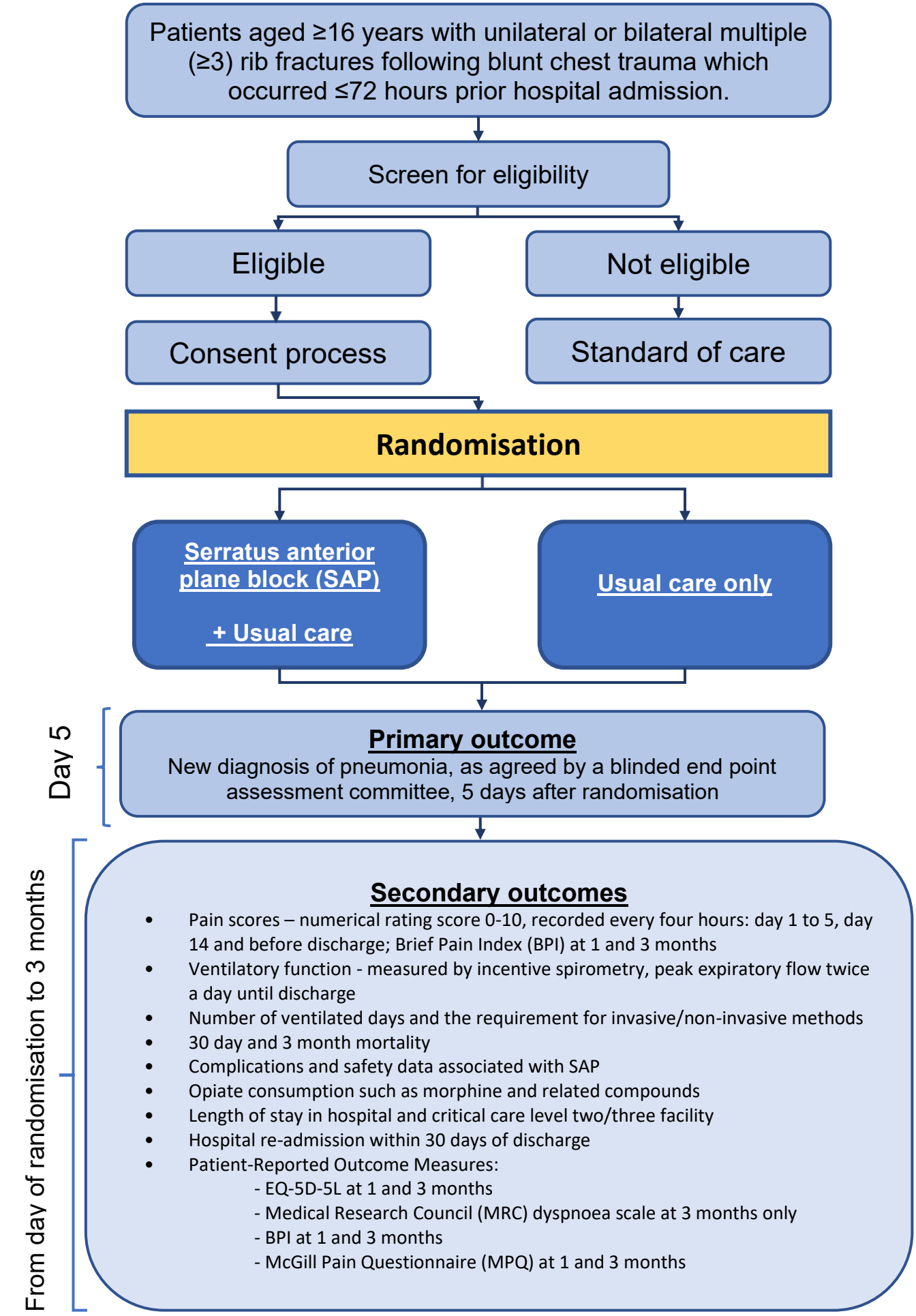


Table of Contents

1. Background and Rationale 14

1.1. Background 14

1.1.1. Burden of the condition 14

1.1.2. Current Practice and existing research 14

1.2. Trial Rationale 14

1.2.1. Justification for participant population 15

1.2.2. Justification for design 15

1.2.3. Choice of intervention 15

1.2.4. Justification of choice of the primary outcome 16

2. Aims and Objectives 17

2.1. Internal Pilot 17

2.2. Main Trial Objectives 17

2.2.1. Primary objective 17

2.2.2. Secondary objectives 17

3. Trial Design and Setting 18

3.1. Trial Design 18

3.2. Trial Setting 18

3.3. Assessment of Risk 18

4. Eligibility 19

4.1. Inclusion Criteria 19

4.2. Exclusion Criteria 19

4.3. Co-enrolment 20

5. Consent 21

5.1. Consent Procedure 21

5.1.1. Potential participant with the capacity to give written consent 21

5.1.2. Potential participant lacking capacity to give consent (for sites in England and Wales) 22

5.1.3. Personal consultee 22

5.1.4. Nominated consultee 22

5.1.5. Potential participant lacking capacity to give consent (for sites in Scotland) 22

5.1.6. When participant regains capacity 23

5.2. Consent documentation 23

5.3. On-going consent 23

5.4. Participants who do not survive 23

5.5. consent to link routine health data 24

5.6. Consent to blood sample collection 24

6. Recruitment, Enrolment and Randomisation 25

6.1. Screening and Identification 25

6.2. Randomisation 25

6.2.1. Randomisation System 25

6.2.2. Randomisation procedure 25

6.2.3. Randomisation method 26

6.3. Blinding 26
6.4. Informing the participant's General Practitioner (GP) 26
7. Trial Intervention 27
7.1. Trial intervention 27
7.1.1. Usual Care 27
7.1.2. SAP 27
7.1.3. Training on SAP 27
8. Outcome Measures 28
8.1. INTERNAL Pilot Trial Outcomes 28
8.2. Main Trial Outcomes 28
8.2.1. Primary Outcome 28
8.2.2. Secondary Outcomes 28
9. Trial procedures 30
9.1. Schedule of Assessments 30
9.1.1. Screening 30
9.1.2. Baseline (Day 0: within 48 hours of randomisation) 30
9.1.3. During hospital stay (Day 1 (from time of randomisation) until discharge from hospital) 31
9.1.4. After discharged from hospital (Month 1 and 3 from time of randomisation) 31
9.1.5. Blood sampling for future research 32
9.2. Participant Withdrawal 33
9.2.1. Level of participation 34
9.2.2. Withdrawal documentation 34
10. Adverse Event Reporting 35
10.1. definition 35
10.2. AE/SAE Reporting period 35
10.3. Adverse eventS in eraser 36
10.4. serious adverse events in eraser 36
10.4.1. SAEs not requiring reporting 36
10.4.2. SAEs requiring non-expedited reporting 37
10.4.3. SAEs requiring expedited reporting 37
10.4.4. Follow up of pregnancy outcomes for potential SAEs 38
10.4.5. Assessment of causality 38
10.4.6. SAE Reporting Procedure on SAE Form 39
10.4.7. Provision of follow-up information 39
10.4.8. Assessment of expectedness of an SAE by CI 39
10.5. Reporting of SAE by TRial office 40
10.5.1. Data Monitoring Committee 40
10.5.2. REC, Sponsor and University of Birmingham (UoB) 40
10.5.3. Sites 40
11. DATA HANDLING AND RECORD KEEPING 41
11.1. Data Management 41
11.1.1. Case Report Form Completion 41
11.1.2. Patient Completed Questionnaires 42

11.1.3. Source Data 42
11.2. Data Security 43
11.3. Archiving 44
12. QUALITY CONTROL AND QUALITY ASSURANCE 45
12.1. Site Set-up and Initiation 45
12.2. Monitoring 45
12.2.1. Onsite Monitoring 45
12.2.2. Central Monitoring 45
12.3. Audit and Inspection 45
12.4. Notification of Serious Breaches 46
13. END OF TRIAL DEFINITION 46
14. STATISTICAL CONSIDERATIONS 47
14.1. Sample Size 47
14.2. Analysis of Outcome Measures 47
14.2.1. Primary Outcome Measure 47
14.2.2. Secondary Outcome Measures 47
14.2.3. Subgroup Analyses 48
14.2.4. Missing Data and Sensitivity Analyses 48
14.3. Planned Final Analyses 48
15. Health Economics 49
15.1. aim 49
15.2. Economic evaluation 49
15.2.1. Within trial economic evaluation 49
15.2.2. Model based economic evaluation 49
16. Trial Organisational Structure 50
16.1. Sponsor 50
16.2. Coordinating Centre 50
16.3. Trial Management Group 50
16.4. Co-investigator Group 50
16.5. Trial Steering Committee 50
16.6. Data Monitoring Committee 50
16.7. Blinded End Point Review Committee 50
16.8. Finance 51
17. Ethical Considerations 51
18. Confidentiality and Data Protection 51
19. Financial and Other Competing Interests 52
20. Insurance and Indemnity 52
21. Post-Trial Care 52
22. Access to the Final Trial Dataset 52
23. Publication Policy 53
24. Reference List 54
25. APPENDICES 56

25.1. Abbreviations.....56

1. BACKGROUND AND RATIONALE

1.1. BACKGROUND

1.1.1.Burden of the condition

Patients with Multiple Rib Fractures (MRF) contribute up to 10% of hospital admissions to Major Trauma Centres (MTC) in the UK (1). Often this leads to a significant risk of morbidity and mortality from initial thoracic injury or a consequence of secondary insults related to their rib fractures. The pain caused by MRF prevents patients from coughing and moving effectively, leaving them unable to clear secretions and increasing the risk of developing severe infections such as atelectasis, pneumonia, sepsis, and acute respiratory distress syndrome. Pneumonia is a complication of MRF and is diagnosed in 11-31% of MRF patients, increasing their mortality risk (2-4). These complications can delay the Intensive Care Unit (ICU) and hospital discharge and cause a long-term impact on mortality and morbidity. Conservatively, MRF cost approximately £7000 per patient in the acute setting (5) and long-term costs are substantially more because of the loss of societal productivity. Therefore, it remains a significant health and economic burden in the UK. 40% of these patients are of working age, and 60% do not return to full-time employment for five years.

1.1.2.Current Practice and existing research

Analgesia has been shown to reduce the risk of respiratory complications by enabling deep breathing, cough, and early mobilisation [6, 7, 8]. Regional analgesia with paravertebral catheters (PA) or thoracic epidural (TEA) was considered the 'gold standard' for the management of pain after MRF (9). A national survey conducted by the Chief Investigator (CI) and team demonstrated that the use of regional anaesthesia was limited due to patient factors, associated injuries, and availability of local expertise, with only 18% having access to these regional anaesthetic techniques (2-4). Opiate based pain relief is the current usual care despite its adverse effects like delirium, cough, and respiratory suppression (2-4, 6, 7). Respondents highlighted that the pain was never 'always' controlled. From the survey, it was found that clinicians preferred regional techniques, but barriers to the insertion of PA and TEA prevented their widespread use. The main obstacles were contraindications (69%), skill mix (64%), service and time pressures (52%), and inability to position patients appropriately (48%).

1.2. TRIAL RATIONALE

Patients with MRF require a simple, safe, effective, and universally available analgesic option. Serratus Anterior Plane Block (SAP) is a new technique placed under ultrasound guidance where the catheter is inserted in the lateral chest wall between latissimus dorsi and serratus anterior muscles in the midaxillary line. It blocks the pain caused by MRF and has the potential to provide a simple, easy, safe, and effective analgesic delivery technique in most patients for up to 10 days (10).

The CI, along with collaborators, conducted a cross-sectional cohort study on SAP. Using the Trauma Audit and Research Network database, 203 patients admitted to two Major Trauma Centres with MRF who received regional analgesia between 2016-2018 were included in the study (11). The primary outcome was a change in pain scores (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) and inspiratory volumes (ml) pre- and post-regional analgesia. SAP Catheter, PA Catheter and TEA Epidural were assessed. The results showed an improvement in inspiratory volumes and a reduction in pain scores across all groups. Inspiratory volumes in the SAP group increased from (mean ± standard deviation (SD)) 959 mls ±726 to 1667 mls ± 713 mls ($p<0.001$). Pain scores with SAP block significantly

reduced from moderate/severe to mild/moderate 2.42 ± 0.96 to 1.14 ± 0.81 ($p<0.01$). A similar increase in inspiratory volumes and reduction in pain scores was observed with PA and TEA, but with no statistically significant difference between the groups. These results suggest that post block SAP analgesia improves inspiratory volumes and reduces pain scores similar to PA or TEA. SAP catheters have the potential to radically increase the accessibility of regional analgesia to patients with MRF, similar to the impact of fascia iliac blocks for hip fracture pain. International societies have advocated that a high-quality prospective trial is urgently needed (12). The proposed pragmatic multicentre randomised controlled trial (RCT) comparing SAP to usual care would provide conclusive evidence to address clinicians' moral and ethical dilemmas during pain management after MRF.

An internal literature review performed by our group on the efficacy of SAP analgesia found that there were no published prospective RCTs for SAP analgesia in thoracic trauma (11). A narrative review of the case reports case series and retrospective reviews suggest a significant improvement in pain scores and inspiratory volumes following SAP analgesia, as indicated by our cross-sectional cohort study data (13-15). A second systematic review on the safety of SAP analgesia with the terminology broadened to include postoperative surgical patients returned 6 RCTs that reported no adverse events after SAP analgesia. At the time of review (2022), there were 3 RCTs registered with clinicaltrials.gov (16-18), but their methodology is significantly different to the ERASER Trial. The participants in this trial will better represent the trauma cohort in the UK, with a robust methodology and sufficient power to detect clinically relevant patient-centred outcomes. This pragmatic, multicentre RCT with a stratified approach will ensure the generalisability of results to trauma practice worldwide.

The ERASER Trial aims to answer a vital question for both patients and clinicians with the prospect of improving patient comfort, care and outcome, and costs in the NHS. The results of this study will have a significant impact in 2 different ways:

Patient benefit: if the trial finds that either treatment protocols reduce acute pain and pneumonia, maintains patient safety, and is cost-effective, it will significantly impact the way patients with MRF in the NHS are currently managed.

Change in practice: if SAP is effective, it will lead to a consensus on the preferred usual care for patients with MRF and prompt rapid change to NICE guidance, with the consequential amendment to care pathways and resource use across the NHS. However, importantly if there were no benefit, the trial would provide evidence to stop the use of the ineffective treatment within the NHS.

1.2.1.Justification for participant population

The patients involved in the ERASER Trial will be adult patients (aged ≥16 years) with three or more unilateral or bilateral fractures following blunt chest trauma and admission to the hospital. This patient cohort was selected as they are at high risk of developing post-traumatic complications, including pneumonia.

1.2.2. Justification for design

ERASER is a randomised controlled trial. The insertion of regional anaesthetic catheters and continuous infusions of local anaesthesia cannot be blinded for apparent reasons. This was discussed with the focus group and the multidisciplinary trial team, who agreed to the trial design.

1.2.3.Choice of intervention

In the CI's cross-sectional cohort study (11), SAP block provides comparable, adequate, and effective analgesia to epidural analgesia post-insertion. A 3-arm trial was considered comparing SAP against TEA/PA and opiates individually; however, the group decided against this because exclusively comparing SAP to TEA/PA would significantly reduce recruitment due to restrictions on TEA/PA

insertion due to coagulopathy, head and spinal injuries, comorbidities and use of anticoagulant medications. The current trial will allow better recruitment due to less stringent inclusion/exclusion criteria making the results more applicable and generalisable. This approach also optimises the chance that significant differences in pneumonia rates, mortality and length of stay are identified as the patients with the highest levels of injury and comorbid disease who may benefit most from SAP analgesia are not excluded (19, 20).

1.2.4.Justification of choice of the primary outcome

The Clinical Pulmonary Infection Score (CPIS) is pragmatic, commonly used and provides an easy and reproducible measure of hospital-acquired pneumonia (HAP) (it includes fever, leucocytosis, oxygenation, tracheal secretions, and chest radiograph to diagnose pneumonia). HAP is associated with longer hospital stays, ventilatory support and organ failure. This primary outcome was discussed and accepted as the most relevant clinical outcome in the national survey, Patient and Public Involvement (PPI) meetings, and international rib fracture pain management conference held at Geisingen, Germany (July 2019).

2. AIMS AND OBJECTIVES

The trial aims to evaluate the clinical and cost-effectiveness of SAP with usual care compared with usual care only in adult patients with MRF admitted to the hospital.

2.1. INTERNAL PILOT

There will be a 12-month internal pilot. The aims of the pilot are to assess whether the recruitment rate, randomisation and adherence to the follow-up assessment schedule are feasible. it will:

- Involve sites that receive between 200-300 patients with significant chest injuries (≥3 rib fractures/flail segments) per year
- Recruit 100 patients within 9 months (12% of the total sample) based on an anticipated recruitment rate of 4 patients, per centre, per month

In terms of recruitment, the success of the internal pilot will be based on the traffic light system.

Go: 100% recruitment: progress to the main trial.

Amend: 50-99% recruitment: continuation of recruitment is contingent on the submission (and approval by the funder) of a clear rescue plan.

Stop: <50% recruitment: stop the trial.

Randomisation, adherence to the follow-up schedule and any unforeseen issues, will be reviewed prior to progressing to the main trial, and, if required, amendments to the protocol will be made accordingly.

2.2. MAIN TRIAL OBJECTIVES

2.2.1.Primary objective

To determine whether treating MRF patients with SAP decreases the rates of pneumonia 5 days after randomisation, as defined by a blinded end point review committee using CPIS and all available trial related clinical information.

2.2.2.Secondary objectives

To determine whether treating MRF patients with SAP:

1. Reduces pain - using a numerical rating scale (0-10), recorded every 4 hours on day 1 to day 5, day 14 and discharge. Pain will also be assessed through use of the patient-reported Brief Pain Index (BPI) at one and three months post-randomisation.
2. Improves ventilatory function - measured by incentive spirometry, peak expiratory flow twice a day via the daily assessment log until discharge
3. Reduces the number of days ventilated and the requirement for invasive/non-invasive methods
4. Improves 30 day and 3-month mortality
5. Is safe and not associated with significant complications
6. Impacts opiate consumption such as morphine and related compounds
7. Reduces hospital re-admission within 30 days of discharge
8. Is cost-effective in the NHS setting, this will be assessed through a cost-utility analysis
9. Impacts Patient-Reported Outcome Measures (PROMs) at one- and three-months post randomisation:
    - EQ-5D-5L
    - Medical Research Council (MRC) dyspnoea scale (at 3 months)

- BPI
- McGill Pain Questionnaire (MPQ)

3. TRIAL DESIGN AND SETTING

3.1. TRIAL DESIGN

A pragmatic, multicentre, open-label, 1:1 two-arm allocation concealed RCT with an internal pilot and full economic evaluation.

3.2. TRIAL SETTING

The trial will take place both on wards and ICUs of NHS MTCs in the UK with a track record of participating in critical care research and confirmed access to the MRF patient population.

The pilot trial will consist of several MTC's in the UK that has a high number of trauma patients with ≥3 MRF. On successful completion of the pilot, further sites will be opened for the main trial.

3.3. ASSESSMENT OF RISK

All clinical trials can be considered to involve an element of risk, and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures (SOP), this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care.

ERASER is a non-CTIMP that has been formally risk assessed by BCTU as 'low risk with no higher than the risk of usual care in this setting' on the basis that both the intervention and control arms are already in common usage throughout the UK and the safety profiles are well established.

The assessment and management of risks is detailed in the trial Risk Assessment document. A review of risk will be conducted in accordance with BCTU SOPs throughout the trial.

4. ELIGIBILITY

4.1. INCLUSION CRITERIA

The site PI will be a medically qualified doctor or an appropriately qualified health care professional and will be responsible for maintaining oversight of the confirmation of the eligibility process. In order to be eligible for the ERASER trial, patients must meet the following inclusion criteria:

1. Aged ≥16 years with unilateral or bilateral ≥3 rib fractures following blunt chest trauma
2. The injury occurred ≤72 hours before hospital admission

4.2. EXCLUSION CRITERIA

If any of the following exclusion criteria apply, the patient is not eligible to be randomised into the ERASER trial:

1. Severe traumatic brain injury *with a predicted ventilatory requirement >7 days*
2. Acute quadriparesis
3. Spinal fracture precluding mobilisation
4. Penetrating trauma or open rib fractures
5. Upper airway injury requiring intubation and mechanical ventilation with an expected dependency of more than 5 days *(e.g., tracheal disruption)*
6. Any chest wall injuries that preclude a catheter insertion
7. Not anticipated to survive ≥48 hours
8. Contamination or infection at the site of potential SAP insertion as deemed by the local PI
9. Any contraindication for SAP block catheter insertion as deemed by the local PI
10. Patients of childbearing age who have tested positive for pregnancy[1]

[1] Pregnancy test taken as part of usual care

4.3. CO-ENROLMENT

Due to the emergency nature of this trial, the research team at the site is highly unlikely to be aware if a participant is already participating in a clinical trial. Where a participant is subsequently found to have been participating in a concurrent trial, the site should inform the ERASER Trial Office, who will in turn request that the CI assesses any safety concern or impact on the trial data. The site should follow its local procedure for reporting trial co-enrolment.

Where appropriate, participants in this trial may take part in other observational and selected interventional studies. Co-enrolment will be considered on a case-by-case basis after discussion with the Trial Management Group (TMG) which will take into account statistical considerations and potential impacts on primary and secondary outcomes. The site should contact the ERASER Trial Office should such queries occur to seek advice prior to enrolling the participant.

5. CONSENT

Potential participants with MRF will, by default, be critically ill due to the effects of sedation, possible infection and possible delirium and, therefore, may lack the capacity to consent for themselves. Sites should follow the appropriate consent procedure depending on the potential participant's mental status. Where the potential participant lacks the capacity to consent for themselves, advice will be sought from a consultee (for sites in England and Wales; see section 5.1.2) or consent will be sought from a legal representative (for sites in Scotland; see section 5.1.5. Contact with the potential participant, consultee, or legal representative, to initiate the consent process should be made as soon as practically possible after the initial emergency has passed, taking the utmost care and sensitivity in doing so.

The Principal Investigator (PI) or delegate(s) are responsible for obtaining written informed consent for each participant and/or advice from a consultee or consent from a legal representative. Consent may also be taken by other members of staff at the site (e.g. Research Nurse or Allied Health Professionals) if local practice allows, and this role has been delegated by the PI on the Site Signature and Delegation Log.

Given the urgent nature of the condition, randomisation and intervention should occur on the same or next working day after consent has been taken.

5.1. CONSENT PROCEDURE

5.1.1.Potential participant with the capacity to give written consent

A Participant Information Sheet (PIS) will be provided to facilitate the process of consent. To avoid overwhelming patients already facing a life-threatening condition, a Summary PIS will be provided. Unless the full PIS is requested during consent, it will be provided later when the participant's condition has improved. The PI or delegate will ensure that they adequately explain the aim of the trial, trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the potential participant. They will also explain that participation in the trial is voluntary, and they can refuse to take part or withdraw from the trial at any time without affecting their care.

The potential participant will be given sufficient time to read the PIS, given the opportunity to ask questions, and, if desired, discuss their participation with others beyond the clinical or research team. If the potential participant then expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The consent will document that the participant understands and acknowledges that a copy of the signed ICF will be transferred to the ERASER Trial Office for review. In situations where the potential participant has the capacity and has agreed to join the trial, but is unable to physically sign the ICF (e.g. unable to hold a pen), a witness will countersign the ICF (the witness does not need to be on the Site Signature and Delegation Log).

The PI or delegate will countersign and date the ICF. A copy will be given to the participant, filed in the medical notes and sent to BCTU, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF.

5.1.2.Potential participant lacking capacity to give consent (for sites in England and Wales)

Participants that are eligible to be recruited into the ERASER trial will have suffered significant trauma and as a result may not have the capacity to provide written and informed consent at the time of hospital admission. In such instances, consent can be provided by a personal consultee (see section 5.1.3), or if one is not immediately available, a nominated consultee (see section 5.1.4).

5.1.3. Personal consultee

A personal consultee is defined as a person who cares for the adult lacking capacity or is interested in that person's welfare, but is not doing so for remuneration or acting in a professional capacity.

If the potential participant lacks capacity, the PI or delegate should, in the first instance, seek advice from a personal consultee on whether the potential participant would wish to be included in the trial. A personal consultee is not asked to give consent on behalf of the potential participant but rather to provide an opinion on the views and feelings of the potential participant. They will be given sufficient time to read the Consultee/Legal Representative Information Sheet and provided with ample opportunity to ask questions and discuss with others beyond the clinical or research team.

The consultee must be informed that they are:

- Being asked to advise on the views and feelings they believe the patient would have towards participating in the ERASER Trial
- Free to decide whether they would like to provide this advice
- Provided with sufficient understandable information about the ERASER Trial so that they can provide informed advice

The advice given by personal consultees will be recorded on a Consultee Declaration Form. If/ when the participant regains capacity during the study, the PI or delegate will follow the procedure in section 5.1.6 and confirm ongoing consent.

5.1.4. Nominated consultee

A nominated consultee is defined as a professional who is independent of the trial.

If a suitable personal consultee is not immediately available, advice from a nominated consultee can be recorded instead on the Consultee / legal representative Form. The nominated consultee must be informed on the points specified section 5.1.3.

If/ when the participant regains capacity during the study, the PI or delegate will follow the procedure in section 5.1.6 and confirm ongoing consent.

If the legal representative is of the opinion that participating in the ERASER Trial is not in the best interests of the potential participant, they will not be recruited into the trial and will be provided with usual care without prejudice.

5.1.5.Potential participant lacking capacity to give consent (for sites in Scotland)

In Scotland, where a potential participant is unable to consent for themselves, consent can be provided by a legal representative.

The PI or delegate should ask a legal representative to provide consent on behalf of an adult who lacks capacity to do so themselves. Those who are able to act as a legal representative are patient's welfare guardian or welfare attorney, and if one is not appointed, the patient's nearest relative.

The legal representative must be informed that they are:

- Being asked to give consent on behalf of the incapacitated patient
- Free to decide whether they wish to make this decision or not
- Being asked to consider what the patient would want, and to set aside their own personal views when making this decision
- Given sufficient information, in an understandable form, about the ERASER Trial to ensure that they can make an informed decision

The consent given by the legal representative will be recorded on a Legal Representative Consent Form. If/ when the participant regains capacity during the study, the PI or delegate will follow the procedure in section 5.1.6 and confirm on-going consent.

5.1.6.When participant regains capacity

Where the participant regains capacity, the research team at the site should seek consent from them, at the earliest opportunity, using the current ethically approved PIS and ICF (process outlined in section 5.1.1). The consultee or legal representative should be informed of this at the outset. Should the participant express a view that they no longer wish to take part in the ERASER trial, their opinion will supersede that of the consultee or legal representative.

5.2. CONSENT DOCUMENTATION

Details of the informed consent discussions with the participant, consultee or legal representative will be recorded in the participant's medical notes. This will include the date of discussion, name of the trial, a summary of the discussion, version number of the documents given to the participant/consultee/legal representative, and date consent/advice received. Where consent/advice is obtained on the same day that the trial-specific procedures are due to start, a note should be made in the medical notes as to what time the advice/consent was obtained and procedures started.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution.

5.3. ON-GOING CONSENT

At each visit, the participant's willingness to continue in the trial will be ascertained (through the participant, consultee, or legal representative as appropriate) and documented in the medical notes. Throughout the trial, the participant, consultee or legal representative will have the opportunity to ask questions about the trial.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the decision to continue, the participant, consultee or legal representative will be given time to consider, and if happy to continue, they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

5.4. PARTICIPANTS WHO DO NOT SURVIVE

The most challenging ethical consideration in this trial is related to the inevitable death of some participants. Advice (England, Wales and Northern Ireland) or consent (Scotland) will always be obtained prior the participant being randomised, however in some instances this may have been provided by a nominated consultee (England, Wales and Northern Ireland) or a legal representative

who is not related to the participant (Scotland). Actively seeking out and informing relatives of trial participation is transparent and avoids potential distress should they, in the future, discover that their relative had been involved in research. However, this will impose an additional emotional burden at a time of great distress (e.g., the immediate aftermath of the loss of a relative). Previous and ongoing emergency care studies have used passive information approaches, placing information in publicly accessible locations and in sites likely to be visited by relatives of the participants (hospitals, GP surgeries, the offices of the Registrars of Births and Deaths). Such information contains brief information about the trial and contact details for those wishing to seek further information. This allows a relative to make an individual decision as to whether to seek further information to find out if their relative was part of the trial. ERASER will take this approach and an ethically approved poster will be provided to sites to display (in appropriate locations), for this purpose.

5.5. CONSENT TO LINK ROUTINE HEALTH DATA

There is an additional, optional statement in the ICF/Declaration Form for the participant/consultee/legal representative to acknowledge that they understand that the ERASER Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant/consultee/legal representative will acknowledge that they understand that the ERASER Trial Office might send the participant's name, address, date of birth and NHS number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the ERASER Trial Office. The acknowledgement by the participant/consultee/legal representative will also allow access to other new central UK NHS databases that will appear in the future. This will enable the ERASER Trial Office (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without further contacting the trial participants.

5.6. CONSENT TO BLOOD SAMPLE COLLECTION

Participant/consultee/legal representative will be asked to acknowledge that they understand a blood sample will be collected and stored for analysis as part of future ethically approved research. The blood sample will be spun and stored at the site until batch transfer at appropriate intervals to the laboratory at the University of Birmingham for storage.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. SCREENING AND IDENTIFICATION

All patients who have suffered blunt chest trauma with MRF admitted to ward and critical care will be screened daily for eligibility. The site research team, who form part of the patient's clinical care team, will review patient's medical records to ascertain whether the patient meets the eligibility criteria. This process may be assisted by the Research Nurses/Practitioners employed or who hold an honorary contract with the site.

A medically qualified doctor, or an appropriately qualified healthcare professional, who has been delegated the task on the Site Signature and Delegation Log will confirm eligibility before randomisation. Potential participants who are deemed eligible will be approached by their clinical care team for consent as described in section 5. The patient will then be randomised and baseline data will be collected.

Details of all patients approached about the trial will be recorded on the Participant Screening/Enrolment Log, which will include data on the number of patients meeting the inclusion criteria but not entered into the trial and reasons for non-enrolment. The Participant Screening/Enrolment Log will be kept in the ISF, and should be available to be sent to the ERASER Trial Office upon request.

6.2. RANDOMISATION

6.2.1.Randomisation System

Randomisation will be provided by a secure online randomisation system at the BCTU (available at https://bctu-redcap.bham.ac.uk), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to site staff that have been delegated the role of randomising patients into the trial as detailed on the trial Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from very short periods of scheduled maintenance. If delegated site staff have lost their username or password, the ERASER Trial Office should be contacted directly via email or telephone using the contact details outlined on page 5 of the protocol. In rare instances that the database is unavailable, researchers can call the telephone toll-free randomisation service (0800 953 0274) Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham closed days.

Please note: it is expected that the primary route for participant randomisation will be via the online randomisation system.

6.2.2.Randomisation procedure

After eligibility for randomisation has been confirmed and informed consent has been received from the participant, consultee or legal representative, the participant can be randomised into the trial using the online randomisation system (see section 6.2.1). Randomisation forms, which contain fields outlining all of the necessary information, including inclusion and exclusion criteria, will be made available and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation form must be answered prior to randomisation; a Trial Number

will then be allocated. If data items are missing, randomisation will be suspended but can be resumed once the information is available.

Following randomisation, a confirmatory email will be sent to the PI, ERASER Trial inbox and the individual randomising the participant.

The site research team should add the participant to the trial Participant Recruitment and Identification Log, which links participants with their Trial Number. The PI must maintain this document securely in strict confidence and it must not be submitted to the ERASER Trial Office.

6.2.3.Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either the Intervention arm: SAP plus usual care or control arm: usual care only. A minimisation algorithm will be used within the online randomisation system to ensure balance in the intervention allocation over the following variables:

- Gender (male, female)
- Age (<60 years, ≥60 years)
- Centre (NHS Trust name)
- Pulmonary contusion (unilateral, bilateral)
- Rib fracture (displaced, non-displaced)
- Anatomical location of fracture (anterior, lateral, posterior)
- Presence of flail segment (yes, no)

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at the ERASER Trial Office.

6.3. BLINDING

ERASER is an open label trial and is not blinded at the patient or investigator level. However, the trial will utilise a blinded end-point review committee (BERC) to assess the primary outcome to determine the rate of pneumonia 5 days after randomisation using CPIS and all available trial related clinical information.

6.4. INFORMING THE PARTICIPANT'S GENERAL PRACTITIONER (GP)

With consent from the participant/legal representative or no objection from the consultee, the participant's GP will be notified that they are in the ERASER trial, using the trial specific ERASER GP Letter.

7. TRIAL INTERVENTION

7.1. TRIAL INTERVENTION

Participants randomised to the control arm of the ERASER trial will receive the usual care for analgesic management for patients with MRF as per local standard practice. Whereas patients randomised to the intervention arm will receive SAP plus usual. In order to be adherent to the intervention arm of the trial, the SAP catheter has to be inserted for a **minimum of 24 hours**, if the catheter is removed prior to this, it should be classified as a failure of intervention and a change of status form should be completed accordingly. There is no trial mandated maximum duration for how long a SAP catheter should remain in place, both monitoring and removal should be in line with local standard practice.

7.1.1.Usual Care

The current usual care for patients with MRF may consist of twice a day physiotherapy, multimodal analgesia (e.g. gabapentin, non-steroidal anti-inflammatories, opioids), incentive spirometry and rib fixation. The content of usual care may vary slightly across NHS Trusts, which reflects the real-world variation in standard practice.

7.1.2.SAP

SAP catheter (CE marked and produced for peripheral nerve blocks) is inserted, under ultrasound guidance, in the lateral chest wall between latissimus dorsi and serratus anterior muscles in the midaxillary line. Local anaesthetic will be infused, using a continuous infusion pump, at a rate consistent with local standard practice. Depending on the patients body weight, concentration of long acting local anaesthetic and the duration of infusion, we recommend a rate of infusion between 5-25ml/hr.

It is expected that there will be some variation in the technical aspects of block insertion. This represents real-world variation in anaesthetic practices and will not contribute to bias as the randomisation procedure will ensure balance across groups by centre. Location and dose of anaesthetic will be captured on a CRF. The technique for insertion of SAP catheters, initial local anaesthetic bolus dose and maintenance regime will be according to local policy.

7.1.3.Training on SAP

Each site will receive full training for implementing the SAP catheter. This will consist of a competency-based mandatory programme that includes:

- A competency questionnaire completed by principle investigators before enrolment as a site to confirm the understanding and ability to deliver this trial. The CI will review the completed competency questionnaire, and sign off to confirm site competency.
- Successful completion of an online E-learning package[3]
- If required, 'hands-on' ultrasound scanning sessions of critical care and trauma patients facilitated by the trial team

[3] https://www.learningapps.co.uk/moodle/xertetoolkits/play.php?template_id=1965

All anaesthetics and analgesia will be taken from standard pharmacy stock and administered according to local policy. This trial does not fall under the Medicines for Human Use (Clinical Trials) Regulations 2004; segregated stocks for trial use and specific trial labelling are not required. Temperature monitoring should follow local pharmacy practice and deviations need not be reported to the ERASER Trial Office.

8. OUTCOME MEASURES

8.1. INTERNAL PILOT TRIAL OUTCOMES

The outcomes for the internal pilot are as follows:

1. Confirmation of the projected recruitment rate as determined by the traffic light system
2. Appropriateness of the randomisation method
3. Adherence to the follow-up schedule

8.2. MAIN TRIAL OUTCOMES

8.2.1.Primary Outcome

New diagnosis of pneumonia, as agreed by a blinded end point assessment committee[4], 5 days after randomisation.

8.2.2.Secondary Outcomes

The secondary outcomes for the ERASER trial are as follows:

1. Reduces pain
    - Numerical rating scale (0-10), recorded average every 4 hours on days 1 to 5, day 14 and before discharge.
    - Patient reported brief pain index (BPI) at 1 and 3 months post randomisation.
2. Improves ventilatory function
    - Incentive spirometry peak expiratory flow twice a day
3. Reduces the number of days ventilated and the requirement for invasive/non-invasive methods
    - Number of days ventilated
    - Type of ventilation – invasive/non-invasive
4. Improves mortality
    - Mortality measured at 1 and 3 months post randomisation
5. Is safe and doesn't have unforseen Complications
    - Measured by SAEs review from randomisation until discharge
6. Impacts opiate consumption such as morphine and related compounds
    - Participant opiate consumption measured at discharge and 3 months post randomisation
7. Reduces length of hospital stay
    - Length of stay in hospital
    - Length of stay in critical care level two/three facility
8. Reduces hospital re-admission within 30 days of discharge
    - Measured by any hospital re-admission within 30 days of discharge

[4] The blinded end point review committee will make their diagnosis based CPIS data and all available trial related clinical information

9. Impacts Patient-Reported Outcome Measures:
    - EQ-5D-5L at 1 and 3 months post randomisation.
    - MRC dyspnoea scale at 3 months post randomisation.
    - BPI at 1 and 3 months post randomisation.
    - SF-MPQ-2 at 1 and 3 months post randomisation

9. TRIAL PROCEDURES

9.1. SCHEDULE OF ASSESSMENTS

9.1.1.Screening

Details of the screening are described in section 6.1, screening assessments will include:

- Daily review of patients who have suffered blunt chest trauma
- Review of the patients medical records
- Confirmation of eligibility criteria
- Completions of screening logs

9.1.2.Baseline (Day 0: within 48 hours of randomisation)

Once consent has been obtained, the following will be recorded prior to randomisation and participant receiving the allocated intervention:

- Relevant medical history (pre-admission details; treatments given to fractures prior to hospital admission)
- Charleson Comorbidity Index
- Basic demographic data
- Details of injury
- Current medication (concomitant medication; analgesic medication; other medication/treatments)
- Routine Assessments:
    - Injury severity scores (Abbreviated injury scale (AIS), frailty score, CPIS, Sequential organ failure assessment (SOFA))
    - ICU and/or hospital admission status
    - Mechanism of injury (pulmonary contusion, anatomical location of fracture, presence of flail segment) and details of other injuries on body
    - Overview of analgesic and other medication
    - Body temperature at hospital
    - Lung function assessments including FEV1 and FVC
    - Chest x-ray (CXR) interpretations, if any (new or progressive infiltrate characteristic of pneumonia or a new consolidation)
    - Tracheal secretions
    - Oxygenation
    - A pregnancy test will be carried out on patients of childbearing potential age, as per usual care
    - CPIS
    - Covid-19 diagnosis and treatment
- Routine laboratory tests: (WBC; white cell count, CRP; C-reactive Protein; culture of tracheal aspirate)
- EQ-5D-5L
- Rating of pain (VAS)
- Blood samples (see section 9.1.5)

The participant will be randomised, and the allocated intervention will begin. The site research team will start to monitor and record any AEs and SAEs as described in section 10.

9.1.3.During hospital stay (Day 1 (from time of randomisation) until discharge from hospital)

The following data will be collected **daily** from the time of randomisation, in line with the routine collection of usual care data:

- Current medication (concomitant medication; analgesic medication; other medication/treatments)
- Lung function assessments.
- FEV1 and FVC to be collected twice per day
- Rating of pain (VAS) - every 4 hours on day 1-5, then on day 14 and at discharge
- Body temperature
- SOFA
- CPIS – Day 5 only
- CXR interpretations
- Tracheal secretion
- Oxygenation
- Rating of pain (VAS) - every 4 hours on day 1-5 , then on day 14 and at discharge
- Critical care minimal data set
- Intervention insertion date/time (only recorded on the date of insertion)
- Intervention removal date/time (only recorded on the date of removal)
- Failure of intervention (i.e. SAP Catheter could not be inserted or removed within 24 hours)
- Routine laboratory tests: (WBC, CRP, culture of tracheal aspirate)
- ICU and/or hospital admission status
- Organ dysfunction through use of the SOFA score
- Other medications or treatments required for MRF
- Adverse events
- Survival status
- Blood samples (see section 9.1.5)

9.1.4.After discharged from hospital (Month 1 and 3 from time of randomisation)

The following will be collected by the site research team after the participant has been discharged from the hospital:

- EQ-5D-5L
- Resource usage
- MRC dyspnoea scale at 3 months only
- BPI
- SF-MPQ-2
- Charleson Comorbidity Index
- Adverse events
- Survival status

These data can be obtained from the hospital's data management systems or via telephone interview with the participant.

9.1.5.Blood sampling for future research

In anticipation of future studies, blood will be collected and spun from participants who have provided consent (either for themselves or where consent/ an opinion has been sought from a legal representative or consultee). These samples will be taken within 24 hours of randomisation, day 5 (± 24h) and day 14 (±24h) if the participant is still admitted and at discharge. The blood sample should be stored at -80°C, and eventually shipped in batches to the laboratory at the University of Birmingham. Full instruction of sample preparation and shipment will be available in a separate Work Instruction.

Table 1: ERASER Trial Schedule of Assessment

Visit	**Screening**	**Baseline**	**Days during hospital**				**At discharge**	**Months post-Randomisation**	
	-	**Day 0**	**1-5**	**6-13**	**14**	**15+**	-	**1**	**3**
Time window	≤ 72 hours	≤ 48 hours	Daily				± 6 hours from discharge	± 7 days	
Eligibility check	X								
Valid informed consent		X							
Relevant medical history		X							
Basic demographic data		X							
Charleson Comorbidity Index		X						X	X
Current medication		X	X	X	X	X	X	X	X
Date & time of injury		X							
Covid-19 diagnosis and treatment		X							
ICU/Ward admission details		X	x	x	x	x	x		
Randomisation		X							
Intervention insertion			X						
Intervention removal			X	X	X	X			
Failure of Intervention		X							
Date of discharge							X		
Routine physical exam:									
Pregnancy test		X							
Body temperature		X	X	X	X	X			
AIS		X							
Frailty score		X							
SOFA		X	X	X	X	X			
CPIS		X	X	X	X	X			

Visit	Screening	Baseline	Days during hospital				At discharge	Months post-Randomisation	
	-	Day 0	1-5	6-13	14	15+	-	1	3
Time window	≤ 72 hours	≤ 48 hours	Daily				± 6 hours from discharge	± 7 days	
Mechanism of injury		X							
Other injury details		X							
Lung function tests (FEV1, FVC **twice per day**)		X	X	X	X	X			
CXR interpretation (if any)		X	X	X	X	X			
Tracheal secretion		X	X	X	X	X			
Lung function assessments		X	X	X	X	X			
Oxygenation		X	X	X	X	X			
Pain rating (VAS **at every 4 hours**)		X	X		X		X		
Critical care minimal data set			X	X	X	X			
Routine bloods (CRP, WBC, Bacteria culture)		X	X	X	X	X			
Analgesic medication		X	X	X	X	X	X		
Concomitant medication		X	X	X	X	X	X		
Adverse events			X	X	X	X	X	X	X
Survival status			X	X	X	X		X	X
Patient reported outcome measures (PROMs) – Interview administered									
Resource usage								X	X
EQ-5D-5L		X						X	X
MRC dyspnoea scale									X
SF-MPQ-2								X	X
BPI								X	X
Blood samples for future studies:		X	X		X		X		

9.2. PARTICIPANT WITHDRAWAL

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and the participants/consultee/legal representatives should be asked about their ongoing willingness to continue participation at all visits.

Participant/consultee/legal representative should be aware from the beginning that the participant can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Participants who subsequently become ineligible following randomisation should be followed up according to all trial processes and will still have their data analysed, unless the participant/consultee/legal representative explicitly change the level of participation.

9.2.1.Level of participation

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant no longer wishes to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant no longer wishes to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

9.2.2.Withdrawal documentation

The change of level in participation within trial (date, reason, and category of status change) should be clearly documented in the source documents and on the Change of Status CRF. Participant/consultee/legal representative can change the level of participation without giving a reason, although a reason would be useful in the pilot to help assess whether it is related to the design of the trial.

10. ADVERSE EVENT REPORTING

10.1. DEFINITION

The recording and reporting of Adverse Events (AEs) will be in accordance with the the Principles of Good Clinical Practice (GCP) as defined by the UK Policy Framework for Health and Social Care (2017) and the requirements of the Health Research Authority (HRA).

Definitions of different types of AEs are listed in table 2.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity, seriousness and causality (relatedness) with reference to the ERASER Protocol.

Table 2: Types of Adverse Events and Definitions

Type of events	Acronym	Definition
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening[5] • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator[6]
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

10.2. AE/SAE REPORTING PERIOD

The reporting period for AEs and Serious Adverse Events (SAEs) in the trial will be from the day that the trial intervention was started until the end of the trial follow up period.

[5] The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

[6] Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the above definitions.

10.3. ADVERSE EVENTS IN ERASER

Participants that meet the eligibility criteria for the ERASER Trial will likely have suffered significant trauma and as a result may experience numerous AEs. As these events are well characterised, it is highly unlikely that these AEs will reveal any new safety information relating to the trial intervention, SAP. Due to this, events that meet the definition of an AE but not an SAE (see table 2) will not be required to be reported to the trial team, these AEs should however be recorded as per local practice.

10.4. SERIOUS ADVERSE EVENTS IN ERASER

It is recognised that the frequency of SAEs in this participant population may be high. Many of these SAEs will be anticipated due to the potential severity of the trauma experienced by the participant. We have therefore outlined anticipated SAEs that do not require reporting and anticipated SAEs that do not require expedited reporting. For all SAEs, the PI or delegate must do one of the following:

- **Record safety reporting-exempt SAEs** in the medical notes but not report them to the Trial Office on an SAE form as per Table 3.
- **Report SAEs in a non-expedited manner** to the Trial Office for the pre-defined subset of SAEs as per Table 4.
- **Report SAEs in an expedited manner** (within 24 hours of the site research team becoming aware of the event) to the Trial Office for SAEs not covered by the above 2 categories as per Table 5.

Note: when an SAE occurs at the same hospital at which the participant is receiving the trial intervention or is being followed up for trial purposes, processes must be in place to make the site research team aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.4.1. SAEs not requiring reporting

Several events that meet the definition of an SAE will not require reporting on the trials dedicated SAE form. If any of the events outlined below in table 3 occur during an individual's participation, from the date that trial intervention started through to end of follow-up, reporting the event on a SAE form is not required as the SAE is not considered to be critical to evaluations of the safety of the trial.

Table 3: SAEs that do not require reporting

Expected SAE	**Process**
Pre-planned hospitalisation	Document in medical notes only
SAEs relating to a pre-existing medical condition or those that have occurred as a result of the participants injuries which are unrelated to MRF	Document in medical notes only

All events which meet the definition of serious must be recorded in the participant medical notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

10.4.2. SAEs requiring non-expedited reporting

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition), and the SAE, may be known. That is, such events are protocol-defined as "expected".

Such events should still be recorded by the site research team in the participant's medical notes and reported to the ERASER Trial Office, but it does not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. These SAEs can be reported alongside follow up CRFs at 1 or 3 months post randomisation. These expected SAEs are listed in Table 4 below.

Table 4: ERASER Trial SAEs requiring non-expedited reporting

Expected SAE ID	Expected SAE	Process
01	Hospital admissions lasting less than 24 hours	Report on SAE Form and provide to the ERASER Trial Office along with follow-up CRFs.
02	Death - The cause of which is unrelated to intervention	
03	Organ failure – as indicated by SOFA score	
04	Infection to insertion site	
05	Sepsis	
06	Septic shock	
07	Failure of extubation attempt	
08	New clinical diagnosis of pneumonia	
09	Primary cardiac bradyarrythmias and tachyarrythmias	

10.4.3. SAEs requiring expedited reporting

All SAEs not listed in section 10.4.1 and 10.4.2 must be reported to the ERASER Trial Office on a trial specific SAE Form within 24 hours of the site research team becoming aware of the event. Examples of SAEs that would require expedited reporting can be found in the table 5 below.

Please note: This list is **not** exhaustive.

Table 5: Examples of ERASER Trial SAEs that require expedited reporting

Expected SAE	Process
Anaesthetic toxicity	Report on SAE Form and provide to the ERASER Trial Office within 24 hours of becoming aware of the event.
Primary cardiac bradyarrythmias and tachyarrythmias where local investigators believe the cause local anaesthetic	

10.4.4. Follow up of pregnancy outcomes for potential SAEs

Known pregnancy at the time of randomisation is an exclusion criterion, however, in the unlikely event that a participant becomes pregnant during the course of the trial, this should be reported via the trial-specific Pregnancy Notification Form. There is no identified risk of congenital anomalies or birth defects in the offspring of participants as a result of their participation in the trial.

10.4.5. Assessment of causality

When completing the SAE Form, the PI or an appropriately qualified delegate, will be asked to define the nature of the seriousness (see Table 7) and causality (relatedness; see Table 6) of the event.

In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

All events considered possibly, probably or definitely related to the intervention will be reported as 'related'; all events considered to be unlikely or unrelated to the intervention will be reported as unrelated.

The same categorisation should be used when describing AEs and protocol-exempt SAEs in the medical notes.

Table 6: Category and definition of SAE causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

Table 7: Category and definition of event seriousness

Severity	Definition
Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity is transient and resolved without treatment and with no sequelae.
Moderate	A sign or symptom which interferes with the participant's usual activity.
Severe	Incapacity with inability to do work or perform usual activities.

On receipt of a SAE Form, the ERASER Trial Office will forward it, with the unique reference number, to the CI or delegate who will independently* review the causality of the SAE. A SAE judged by the PI or CI (or delegate) to have a reasonable causal relationship ("Related" as per table 6) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the PI

will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

10.4.6. SAE Reporting Procedure on SAE Form

On becoming aware that a participant has experienced a SAE which requires reporting, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the ERASER Trial Office.

For SAEs that are to be reported on a SAE Form, the PI or delegate must complete, date and sign the SAE Form. The completed form, together with any other relevant anonymised documents, should be submitted to the ERASER Trial Office (details below) in the timeline specified in section 10.4.2 and 10.4.3.

To report an SAE, please complete the SAE Form on https://bctu-redcap.bham.ac.uk and notify the trial office at ERASER@trials.bham.ac.uk

Please note: If a paper SAE Form has been completed, the original must be retained in the ISF following entry onto the trial database.

Where an SAE Form has been completed by someone other than the PI initially, the original SAE Form will be required to be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of an SAE Form, the ERASER Trial Office will allocate each SAE a unique reference number and notify the site via email as proof of receipt. The site and ERASER Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the ERASER Trial Office.

10.4.7. Provision of follow-up information

Where a SAE is reported, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the ERASER Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the ERASER Trial Office and the original kept in the ISF.

10.4.8. Assessment of expectedness of an SAE by CI

The CI or delegate will assess all related SAEs for expectedness with reference to the criteria in table 8 below. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

The CI will undertake review of all SAEs and may request further information from the site for any given event(s) to assist this.

Table 8: Category and definition of AE expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information (i.e. ERASER protocol)
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

10.5. REPORTING OF SAE BY TRIAL OFFICE

10.5.1. Data Monitoring Committee

The ERASER Trial Office will submit SAE data for review by the committee, who may request and review any SAEs at the meetings.

10.5.2. REC, Sponsor and University of Birmingham (UoB)

The ERASER Trial Office will submit a progress report to the Research Ethics Committee (REC), Sponsor, and UoB Research Governance Team (RGT) annually, starting 12 months after the date of initial REC favourable opinion. Any electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

All events categorised as Unexpected and Related SAEs will be reported to these parties within 15 days of being notified.

10.5.3. Sites

Details of all unexpected and related SAEs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of such correspondence should be filed in the ISF and Trial Master File (TMF).

11. DATA HANDLING AND RECORD KEEPING

11.1. DATA MANAGEMENT

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial Data Management Plan, which include the processes of data entry and querying.

Data entry will be completed by the sites via a bespoke BCTU trial database (data capture system). Paper versions of the CRFs will be available as an example of the data required to be collected, but they will not replace the trial database.

The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using a data clarification process via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested at least on a monthly basis and maybe more frequent for Critical Data Items.

PI and research team members delegated with the duties of data collection/querying will be given an individual secure login access to the trial database. Training and written work guides on the database will be provided by the ERASER Trial Office at the Site Initiation Visit. The PI will support subsequent training needs at their sites (for example, when new staff join the study), with assistance from the ERASER Trial Office when needed.

Self-evident corrections are not permitted in the ERASER Trial.

11.1.1. Case Report Form Completion

The CRFs will include, but will not be limited to, the following forms in Table 9.

Table 9: ERASER Trial CRFs

Form Name	Schedule for submission
Consent form	As soon as eligibility has been confirmed
Randomisation form	At the point of randomisation
Hospital admission form and Baseline form	Immediately following randomisation (Day 0)
Daily Assessment	Daily until day 30 or discharge
1 month and 3 month Follow-up CRFs	1 month and 3 months post-randomisation
Serious Adverse Event Form	If expedited: emailed within 24 hours of site research team becoming aware of event If non-expedited: emailed within 4 weeks of site research team becoming aware of event
Pregnancy notification Form	As soon as possible after becoming aware of participant's pregnancy
Change of status Form	As soon as possible after the point of notification or death

A CRF should be completed for each individual participant.

In all cases, it remains the responsibility of the PI to ensure that the CRFs have been completed correctly and that the data are accurate.

The trial Site Signature and Delegation Log will identify the research team members with responsibilities for data collection. The delegated staff should ensure the accuracy, completeness and timeliness of the data reported.

Data reported on each form should be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to trial CRF completion guideline.

The following guidance applies to data and partial data:

- Only CRFs provided by the ERASER Trial Office should be used
- Date format and partial dates – all dates should be in the format of DD/MMM/YYYY
- Time format – all times should be in accordance with the 24-hour clock
- Rounding conventions – should be to the nearest whole number: number ending 5-9 to be rounded up; number ending 1-4 to be rounded down.
- Trial-specific interpretation of data fields
- Entry requirements for concomitant medications – use generic names where possible
- Trial specific interpretation of data fields – where guidance is needed, additional information will be supplied
- Repeat laboratory tests if a test is repeated, it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values
- Protocol and GCP non-compliances should be reported to the ERASER Trial Office on discovery

11.1.2. Patient Completed Questionnaires

Participants will be asked to complete the following questionnaires with site staff over the telephone (if discharged from hospital):

- EQ-5D-5L (at 1 and 3 months)
- Use of healthcare resources (at 1 and 3 months)
- MRC dyspnoea scale (at 3 months)
- Brief Pain Index (at 1 and 3 months)
- McGill Pain Questionnaire (at 1 and 3 months)

The questions will be read to the participant verbatim and responses must not be led by the person assisting with the form completion.

Participants should be encouraged to respond to all questions but can decline to answer any of the questions should they wish. If a participant does not wish to answer a particular question, the research team should note this on the eCRF within the notes section.

Site staff can record responses on the corresponding ERASER trial worksheet, and enter the data onto the database after the telephone call has concluded, or they can enter patient responses directly onto REDCap.

11.1.3. Source Data

Source data is defined as all information in the original records and certified copies of the original records (of clinical findings, observations, or other activities in a clinical trial) necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF, these are clearly identified and detailed below in Table 10.

Source data is kept as part of the participants' medical notes generated and maintained at site.

Table 10: ERASER Trial source data

Data	Source
Participant Reported Outcomes	These are obtained from the participant via interview with site research staff, site staff will the transcribe patient responses onto eCRFs which are the source data.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with local standard practice.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant medical notes. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Health economics data	Data obtained by interview directly with the participant for transcription onto the eCRF. The original eCRF is the source. Data obtained using the hospital health data system, the participant's medical notes will be the source.
Recruitment	The original record of the randomisation is the source. It is held on UoB servers as part of the data capture system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the participant's medical notes.

11.2. DATA SECURITY

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of personal data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The ERASER Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with the UoB policies.

The trial database system incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data.
- Network security measures: including site firewalls, antivirus software, and separate secure network protected hosting.
- System Management: the system will be developed, implement and maintained by the Programming Team at the Trial Office.
- System Design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Trial Office at UoB.
- System Audit: The system will benefit from the following internal/external audit arrangements:
    - Internal audit of the system

- Periodic IT risk assessment
- Data Protection Registration: UoB Data Protection Registration number is Z6195856.

11.3. ARCHIVING

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, participants' medical notes/trial records, copies of CRFs etc.) at their site are securely retained for the contractual period. Archiving will be authorised by the Trial Office on behalf of the Sponsor following submission of the end of trial report. No documents should be destroyed without prior approval from the ERASER Trial Office.

The TMF will be stored at the ERASER Trial Office for at least 3 years after the end of trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years. The ERASER Trial Office has standard processes for both hard copy and computer database legacy archiving.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. SITE SET-UP AND INITIATION

All PIs will be asked to sign the necessary agreements, including a trial specific Site Signature and Delegation log between the PI and the ERASER Trial Office, and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the ERASER Trial Office of any changes in the site research team.

Prior to commencing recruitment, each site will undergo a process of site initiation, either a remote or in-person meeting, at which key members of the site research team are required to attend. The meeting will cover aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2. MONITORING

The central and on-site monitoring requirements for this trial have been developed in conjunction with the Risk Assessment (RA) and are documented in the Monitoring Plan (MP).

12.2.1. Onsite Monitoring

All sites will be monitored in accordance with the RA and MP. Any monitoring activities will be reported to the ERASER Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, e.g., poor site performance. PIs and research teams will allow the ERASER Trial Office staff access to source documents as requested. The monitoring will be conducted by the ERASER Trial Office or Sponsor staff.

12.2.2. Central Monitoring

The ERASER Trial Office will check received ICFs and monitoring data entered onto eCRFs for compliance with the protocol, data consistency, missing data, and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent electronic Data Clarification Forms (DCF) via REDCap requesting missing data or clarification of inconsistencies or discrepancies.

Source data may be requested for the purpose of central monitoring (e.g., for checking eligibility or endpoints). In such case, documents should be redacted and labelled with the trial number before being sharing with the ERASER Trial Office.

12.3. AUDIT AND INSPECTION

The PI will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The PI will comply with these visits and any required follow up. Sites are also requested to notify the ERASER Trial Office of any relevant inspections or local audits.

12.4. NOTIFICATION OF SERIOUS BREACHES

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the ERASER Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the ERASER Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the ERASER Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or the priniciples of GCP as defined by the UK Policy Framework for Health and Social Care Research, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture, including resolution of data queries. This will allow sufficient time for the completion of protocol procedures, data collection and cleaning. The ERASER Trial Office will notify the REC and Sponsor within 90 days of the end of trial.

Where the trial has terminated early, the ERASER Trial Office will notify the REC within 15 days of the end of trial.

The ERASER Trial Office will provide the REC and Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1. SAMPLE SIZE

Assuming a 15% incidence of pneumonia. To detect a 50% relative percentage difference (down to 7.5%) between intervention groups using the standard method of difference between proportions with 90% power and a type I error rate of 5% (two-sided), a total of 371 participants per group will need to be randomised, 742 in total. Assuming and adjusting for a 10% loss to follow-up/ drop-out rate, 824 participants will need to be recruited.

14.2. ANALYSIS OF OUTCOME MEASURES

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below:

The primary comparison groups will be composed of those randomised to and treated with SAP and Usual Care versus those randomised to and treated with usual NHS Usual Care alone comprising of opiates with or without TEA/PA . In the first instance, all analyses will be based on the intention to treat principle, i.e., all participants will be analysed in the intervention treatment group to which they were randomised irrespective of adherence compliance or other protocol deviations. For all major outcome measures, appropriate summary statistics and differences between groups, e.g. relative risks will be presented, with 95% confidence intervals and p-values from two-sided tests also given. Intervention effects Outcomes Analyses will be adjusted for the minimisation variables listed in section 6.2.3 where possible. These variables will be treated as fixed effects, apart from centre which will be included as a random effect. No adjustment for multiple comparisons will be made.

14.2.1. Primary Outcome Measure

New diagnosis of pneumonia five days after randomisation, will be assessed on whether the SAP arm is superior to the Usual Care arm and follow an intention to treat analysis.

The primary outcome is binary (yes/no) and will be analysed using a mixed effects log binomial regression model which will be used to calculate the adjusted relative risk and corresponding 95% confidence interval, adjusted for the variables listed in section 6.2.3. If this fails to converge alternative models will be use such as the Poisson regression (21) with robust standard errors to estimate the same parameters. The p-value relating to the intervention group parameter as generated by the model estimating relative risk will be presented.

14.2.2. Secondary Outcome Measures

Binary outcomes will be analysed in a similar way to the primary outcome.

Continuous outcomes (e.g. number of ventilated days) will be analysed using linear regression methods if the outcome is sufficiently normally distributed (or where the data can be suitably transformed), to calculate an adjusted mean difference and 95% confidence interval. The p-value relating to the intervention group parameter as generated by the model estimating mean difference will be presented.

Mortality data, will be analysed using Cox proportional hazard techniques given the assumptions of proportionality are met, and an adjusted hazards ratio with a 95% confidence interval will be presented.

All secondary outcome confidence intervals will be interpreted cautiously given the potential for multiplicity.

14.2.3. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 6.2.3) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include the imputation process for the primary outcome which will utilise patient recorded characteristics like age, gender and also centre. A cycle of 5 imputations will be considered and pooled results from these will be used (22). Full details will be included in the Statistical Analysis Plan.

14.3. PLANNED FINAL ANALYSES

The primary analysis for the study will occur once all participants have completed the 3-month post-randomisation assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the 3 month assessment and no further.

15. HEALTH ECONOMICS

A separate Health Economic Analysis Plan will be produced which will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

15.1. AIM

To determine the cost-effectiveness of SAP and usual care compared to usual care alone over 3 months.

15.2. ECONOMIC EVALUATION

15.2.1. Within trial economic evaluation

To assess the cost-effectiveness of SAP plus usual care compared to usual care alone, a cost-consequence analysis will initially be reported, describing all the important results relating to resource use, costs and outcomes. Subsequently a cost-utility analysis will be undertaken from an NHS/Personal Social Services (PSS) perspective to determine the cost per Quality adjusted life year (QALY) gained of SAP plus usual care compared to usual care alone over a 3-month period.

Resource use information will be obtained on all healthcare utilisation (primary care and secondary care) and will be obtained mainly from participant questionnaires. Unit costs will be obtained from standard sources and healthcare providers including the British National Formulary (BNF) (23), PSSRU publication on Unit Costs of Health and Social Care (24) and NHS Reference costs (25).

Mean costs and outcomes will be estimated for both the SAP plus usual care and usual care only arms. Cost data are likely to be skewed, therefore, non-parametric comparison of means (e.g., bootstrapping) will be undertaken. Multiple imputation techniques will be used to deal with missing costs and outcomes, in order to ensure that all eligible trial participants are included in the analysis.

Incremental cost-effectiveness ratios (ICERs) will be calculated and cost-effectiveness acceptability curves will be presented to estimate the probability that SAP plus usual care is cost-effective for different willingness to pay thresholds.

15.2.2. Model based economic evaluation

To assess the long-term cost-effectiveness of SAP plus usual care compared with usual care alone, a decision analytic modelling approach (Markov model) will be used to determine the cost per additional QALY gained for SAP plus usual care compared with usual care alone from an NHS/Personal social services perspective. Data from the main trial and other published sources will be used to populate the model. Deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters. Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by conducting a probabilistic sensitivity analysis to estimate cost-effectiveness acceptability curves.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1. SPONSOR

The Sponsor for this trial is the University of Birmingham (UoB).

16.2. COORDINATING CENTRE

The trial coordinating centre (ERASER Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at University of Birmingham.

16.3. TRIAL MANAGEMENT GROUP

The Trial Management Group (TMG) comprises individuals responsible for the day-to-day management of the trial. They include the CI, Co-Investigators (clinical and non-clinical), PPI, Health Economist, Statisticians, Trial Team Leader, Trial Manager, Data Manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial. The TMG will meet frequently to fulfil its function.

16.4. CO-INVESTIGATOR GROUP

The co-investigator group, an extended TMG, will comprise all members of the co-applicant group and members of the TMG to review progress of the trial, troubleshoot and plan strategically.

16.5. TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the trial and will meet as required depending on the needs of the trial.

The TSC will operate in accordance with the trial TSC Charter, which will define the membership and duties/responsibilities. In summary, the role of the TSC is to provide oversight of the trial, and will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC).

16.6. DATA MONITORING COMMITTEE

The role of the independent Data Monitoring Committee (DMC) is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety concerns to the trial. Data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with the trial DMC Charter which will define the membership, roles, and responsibilities. The DMC will meet at least annually with additional meetings arranged if required e.g., recruitment concerns or potential safety issues.

16.7. BLINDED END POINT REVIEW COMMITTEE

The Blinded End Point Review Committee (BERC) will review the relevant medical history and trial data for each of the participants recruited into the trial in order to determine the incidence of pneumonia within the patient cohort. The BERC will not be aware of the treatment allocation of the

trial particpants and trial data will be supplied in confidence by the trial office. The BERCs determination of the incidence of pneumonia will serve as the primary outcome data for the trial.

The BERC will operate in accordance with the trial BERC Charter which will define the membership, roles, and responsibilities. The BERC will meet every three months with additional meetings arranged during periods when the volume of recruitment is higher than expected.

16.8. FINANCE

The research costs of the trial are funded by the National Institute for Health Research (NIHR) Health Technologies Assessment (HTA) Programme (project number: 19/59 – NIHR130632), awarded to Prof. Tonny Veenith of the University of Birmingham. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the SoECAT. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

17. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the the Principles of GCP as defined by the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which includes the Data Protection Act 2018 and the Mental Capacity Act 2005. The protocol will be submitted to, and approved by the REC prior to the start of the trial.

Before any patients are enrolled into the trial, the PI at each site is required to obtain all of the necessary local approvals.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

18. CONFIDENTIALITY AND DATA PROTECTION

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments).

Participants will only be identified by their unique trial identification number and partial date of birth on CRFs and on any correspondence with the ERASER Trial Office. Participant/legal representative or consultee will acknowledge the transfer and storage of the ICF to the ERASER Trial Office. This will be used to perform central monitoring the consent process.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the ERASER Trial Office and Sponsor may be required to have access to participants' medical notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

20. INSURANCE AND INDEMNITY

The UoB has in place clinical trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

21. POST-TRIAL CARE

When the patient has completed follow-up or if they withdraw fully from the ERASER Trial, they will follow their normal usual care pathway.

22. ACCESS TO THE FINAL TRIAL DATASET

The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during the trial will be considered by the ERASER Trial Office.

Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: The trial Sponsor, the relevant TMG and TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

23. PUBLICATION POLICY

Output from this trial will be submitted for publication in peer reviewed journals and presentation at national and international meetings. A final report will be submitted in the NIHR HTA journal. The manuscripts will be prepared by the writing group as defined in the trial Publication Plan.

Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review. Authors should acknowledge that the trial was performed with the support of NIHR HTA, UHB and BCTU. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

The findings of the trial will be made public, which may be shared via the sites, social media, relevant newsletters and trial website. The plan is to develop an infographic leaflet with the PPI to present a summary of the trial findings in an accessible and easy to understand form.

24. REFERENCE LIST

1. Witt, C.E. and E.M. Bulger, Comprehensive approach to the management of the patient with multiple rib fractures: a review and introduction of a bundled rib fracture management protocol. Trauma surgery & acute care open, 2017. 2(1): p. e000064-e000064.
2. Chapman, B.C., et al., RibScore: A novel radiographic score based on fracture pattern that predicts pneumonia, respiratory failure, and tracheostomy. J Trauma Acute Care Surg, 2016. 80(1): p. 95-101.
3. Battle, C.E., H. Hutchings, and P.A. Evans, Risk factors that predict mortality in patients with blunt chest wall trauma: a systematic review and meta-analysis. Injury, 2012. 43(1): p. 8-17.
4. Jensen, C.D., et al., Improved Outcomes Associated with the Liberal Use of Thoracic Epidural Analgesia in Patients with Rib Fractures. Pain Med, 2017. 18(9): p. 1787-1794.
5. Swart, E., et al., Operative Treatment of Rib Fractures in Flail Chest Injuries: A Meta-analysis and Cost-Effectiveness Analysis. J Orthop Trauma, 2017. 31(2): p. 64-70.
6. Bulger, E.M., et al., Rib fractures in the elderly. J Trauma, 2000. 48(6): p. 1040-6; discussion 1046-7.
7. Bulger, E.M., et al., Epidural analgesia improves outcome after multiple rib fractures. Surgery, 2004. 136(2): p. 426-30.
8. Easter, A., Management of patients with multiple rib fractures. Am J Crit Care, 2001. 10(5): p. 320-7; quiz 328-9.
9. Galvagno, S.M., Jr., et al., Pain management for blunt thoracic trauma: A joint practice management guideline from the Eastern Association for the Surgery of Trauma and Trauma Anaesthesiology Society. J Trauma Acute Care Surg, 2016. 81(5): p. 936-951.
10. Blanco, R., et al., Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. 2013. 68(11): p. 1107-1113.
11. Beard,L., et al., Multicenter longitudinal cross-sectional study comparing effectiveness of serratus anterior plane, paravertebral and thoracic epidural for the analgesia of multiple rib fractures. Regional Anaesthesia & Pain Medicine, 2020, 45(5):351-356.
12. Galvagno, S.M., Jr., et al., Pain management for blunt thoracic trauma: A joint practice management guideline from the Eastern Association for the Surgery of Trauma and Trauma Anesthesiology Society. J Trauma Acute Care Surg, 2016. 81(5): p. 936-951.
13. Hernandez, N., et al., A novel technique: Serratus plane block with liposomal bupivacaine for multiple rib fractures. Regional Anesthesia and Pain Medicine, 2015. 40(5).
14. Jenkins, H., I. Abdlaziz, and M. Kadry, Audit on guidelines for management of patients with multiple rib fractures. Anaesthesia, 2018. 73: p. 51.
15. Dieterichs, C., et al., The Therapeutic Activity Goal for Acute Postoperative Pain Management. A A Pract, 2018. 10(6): p. 157-159.
16. Nct, Serratus Anterior Block and Catheter Use in Rib Fractures in the Emergency Department. Https://clinicaltrials.gov/show/nct03711812, 2018.
17. Nct, Serratus Plane Block for Rib Fractures. Https://clinicaltrials.gov/show/nct03664973, 2018.

18. Nct, US-guided SAPB for Rib Fractures in the ED. Https://clinicaltrials.gov/show/nct03619785, 2018.
19. Duch, P. and M.H. Moller, Epidural analgesia in patients with traumatic rib fractures: a systematic review of randomised controlled trials. Acta Anaesthesiol Scand, 2015. 59(6): p. 698-709.
20. Peek, J., et al., Comparison of analgesic interventions for traumatic rib fractures: a systematic review and meta-analysis. Eur J Trauma Emerg Surg, 2018.
21. Zou G. A modified poisson regression approach to prospective studies with binary data. American Journal of Epidemiology. 2004;159:702-706
22. Steele RJ, et al. Simple Estimation of Patient-Oriented Effects From Randomized Trials: An Open and Shut CACE. American Journal of Epidemiology Am J Epidemiol. 2015;182:557-66
23. Joint Formulary Committee. British National Formulary. [82] ed. London: BMJ Group and Pharmaceutical Press; [2021]
24. Curtis, L.A., et al. Unit Costs of Health and Social Care . PSSRU, University of Kent, p. 185.
25. NHS. Reference Costs 2019/2020 NHS England, PAR343. [Internet]. 2021 [Cited Feb 2022]. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/.

25. APPENDICES

25.1. ABBREVIATIONS

AE	Adverse Event
AIS	Abbreviated Injury scale
BCTU	Birmingham Clinical Trials Unit
NBG	British National Formulary
BPI	Brief Pain Index
CE	Conformitè Europëenne
CI	Chief Investigator
CPIS	Clinical Pulmonary Infection Score
CRF	Case Report Form
CRP	C-Reactive Protein
CV	Curriculum Vitae
CXR	Chest x-ray
DCF	Data Clarification Forms
DSA	Data Sharing Agreement
DMC	Data Monitoring Committee
FEV1	First second of forced expiration
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
HAP	Hospital-Acquired Pneumonia
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICERs	Incremental cost-effectiveness ratios
ICU	Intensive Care Unit
ISF	Investigator Site File
MP	Monitoring Plan
MPQ	McGill Pain Questionnaire
MRC	Medical Research Council
MRF	Multiple Rib Fractures
MTC	Major Trauma Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
PA	Regional analgesia with Paravertebral Catheter
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PROMS	Patient-Reported Outcome Measures
PSS	Personal Social Services
QALY	Quality adjusted life year
RA	Risk Assessment
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Serratus Anterior Plane Block
SD	Standard Deviation
SOFA	Sequential organ failure assessment
SOP	Standard Operating Procedure
TEA	Regional analgesia with Thoracic Epidural

TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHB	University Hospitals Birmingham NHS Foundation Trust
UK	United Kingdom
UoB	University of Birmingham
UoB RGT	UoB Research Governance Team
VAS	Visual Analogue Scale
WBC	White Blood Cell counts