STUDY PROTOCOL

The Randomised Evaluation of early topical Lidocaine patches In Elderly patients admitted to hospital with rib Fractures (RELIEF): feasibility trial.

Approvals and IDs	Reference
Protocol version and date	4.0, 04MAR2022
IRAS project ID	285096 and 299793
REC Reference	21/SC/0019 (South Central – Oxford C REC) and 21/SS/0043 (Scotland A REC)
Sponsor	North Bristol NHS Trust (R&I) ref: 4284
ISRCTN	14813929
Funder	National Institute for Health Research (NIHR) Advanced Fellowship NIHR300068
NIHR CRN CPMS	48195

This protocol has regard for the HRA guidance

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Study Website	https://relief.blogs.bristol.ac.uk/

FUNDING AND SUPPORT IN KIND

Funder and support in kind	Financial and non-financial support given
National Institute for Health Research (NIHR) Advanced Fellowship (NIHR300068) NIHR Academy 21 Queen Street Leeds LS1 2TW Telephone: 0113 532 8410 Email: Academy-awards@nihr.ac.uk	Grant funding
Bristol Trials Centre (BTC) Population Health Sciences Bristol Medical School University of Bristol Canynge Hall 39 Whatley Road Bristol, BS8 2PS Telephone: 0117 928 7393 Email: enquiry-brtc@bristol.ac.uk	Methodological expertise
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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AIMS	Accidents Incidents or near Misses
AR	Adverse Reaction
BTC	Bristol Trials Centre
CHI	Community Health Index
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DPA	Data Protection Act
DSA	Data Sharing Agreement
ED	Emergency Department
EDC	Electronic Data Capture
EEA	European Economic Area
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HCP	Healthcare Professional
HRA	Health Research Authority
I.D	Identification
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ISS	Injury Severity Score
ITT	Intention to treat
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PAG	Patient Advisory Group
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
RCT	Randomised Controlled Trial
R&D	Research & Development
RDSF	Research Data Storage Facility
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SAR	Serious Adverse Reaction
SD	Standard Deviation
SEAR	Screened, Eligible, Approached, Randomised
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
UoB	University of Bristol
VAS	Visual Analogue Scale

1 STUDY SUMMARY

Title	The Randomised Evaluation of early topical Lidocaine patches in Elderly patients admitted to hospital with rib Fractures (RELIEF): feasibility trial.	
Study Location	NHS Emergency Departments (EDs) in the UK.	
Study Question	Is it feasible to conduct a multi-centre randomised controlled trial (RCT) to evaluate the use of topical lidocaine patches in older hospitalised patients with rib fractures?	
Study Objective	The objective is to test processes and gather information for the planning of a definitive RCT to evaluate early topical lidocaine patches in older patients admitted to hospital with rib fractures.	
Study Design*	Pragmatic multi-centre 1:1 RCT.	
Main inclusion criteria	• Older adult patients (age ≥ 65 years) presenting to the ED with traumatic rib fracture(s), confirmed radiologically (by chest X-Ray or CT scan) requiring hospital admission for ongoing care.	
Main exclusion criteria	• Serious distracting trauma to other body regions: traumatic brain injury with cognitive impairment, acute spinal column fracture or spinal cord injury, abdominal and lower limb injuries requiring surgery, unstable pelvic fracture. • Requirement for intubation and mechanical ventilation either prehospitally or in the emergency department. • End-stage dementia (adjudicated by the treating clinician); patients with mild to moderate cognitive impairment can be approached. • History of allergy to lidocaine. • Open wounds at the site of patch application. • End-stage liver failure with jaundice. • End-stage heart failure with breathlessness at rest prior to injury. • Those unable to communicate in English language where all reasonable attempts to source translation services are exhausted within the ED. • Patients transferred from non-recruiting units to a recruiting site who have a lidocaine patch applied as part of standard care prior to arrival in the recruiting site.	
Planned sample size	100 (and up to 24 trial participants, and up to 6 people with carer responsibilities (e.g. Personal Consultees, or equivalents in Scotland, or other subsequent carers), in the integrated qualitative study).	
Study Interventions		
Control arm	Usual Care.	
Intervention arm	Up to 3 x 700mg lidocaine patch(es) (Ralvo®) applied over the most painful area of rib injury after first diagnosis as soon as practical within the ED. The patches will be applied once daily for 12-hours in accordance with the manufacturer's (Grünenthal) instructions, followed by a 12-hour patch-free period. Treatment will continue for up to 72 hours or until the time of discharge, whichever is sooner.	
Summary of objectives and outcome measures		
	Objectives	**Outcomes measures**
Feasibility	**A)** the number of eligible patients approached.	Screening log records.
	B) the proportion of approached patients randomised.	Screening log and randomisation records.
	C) attrition (including both failure to complete the trial protocol and loss to follow up).	Research data and withdrawal records.

	D) the proportion of recruited patients for which the primary outcome is available and completeness of each secondary outcome measure.	Research data.
	E) acceptability of the trial processes to clinicians and participants through qualitative interviews.	Qualitative interviews (see Qualitative section 13).
	F) acceptability of outcome measures to patients from interviews.	Qualitative interviews (see Qualitative section 13).
	G) adherence to the intervention.	Inpatient prescribing records.
Clinical**	**1)** 30-day pulmonary complications.	Patient records (including clinical diagnosis of chest infection, pneumonia, pleural effusion or empyema, need for ventilatory support and death secondary to a pulmonary cause if documented).
	2) Incidence of frailty syndromes / analgesia side-effects.	Patient records (including immobility, delirium, and constipation evaluated during the 72-hour intervention period and functional decline at discharge (discharge destination and support required). Development of acute delirium during inpatient stay also at 30-days.
	3) All-cause mortality.	Patient records / electronic patient tracking systems.
	4) Intensive Care admission and length of stay.	Patient records / electronic patient tracking systems.
	5) Hospital re-admission within 30 days.	Patient records / electronic patient tracking systems.
	6) Total length of hospital stay.	Patient records / electronic patient tracking systems.
	7) Total opioid consumption in first 72 hours of admission.	Patient records.
	8) Total pain experienced over the 72 hours period.	Visual Analogue Scale (VAS) and the Abbey pain scale.
	9) Health economic scoping.	EQ-5D-5L questionnaire at baseline (retrospective pre-injury and post injury) and 30-days. ICECAP-O and Chest Trauma Score (RibPROM) questionnaires at 30-days. Plus, information on key costs (see Health Economic section 14).
Study schedule		
Schedule	• Start date (contracting began): 01 January 2020 • Proposed duration: 39 months *(subject to change)* • Proposed end date: 31 March 2023 *(subject to change)*	

**As confirmed by the Medicines and Healthcare products Regulatory Agency (MHRA), this feasibility trial is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) as defined by the EU Directive 2001/20/EC.*

***Clinical endpoints are collected to understand feasibility of data collection to inform a definitive trial and not conduct hypothesis testing.*

2 PATIENT FLOW DIAGRAM

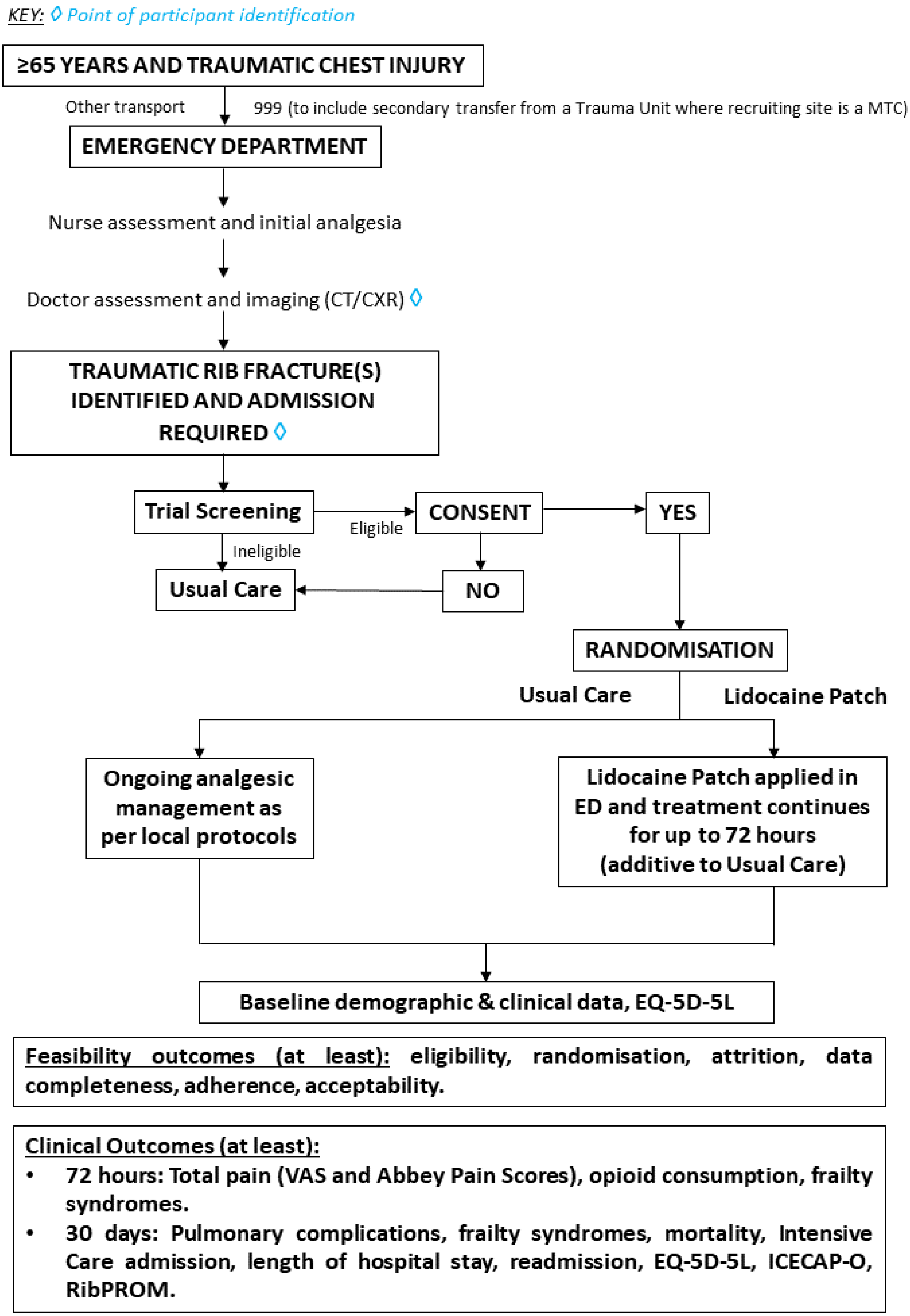


Figure 1 Patient Flow Diagram

3 BACKGROUND AND RATIONALE

Trauma in older patients is increasingly recognised as a significant challenge to healthcare systems (1, 2). Over 20,000 older patients are admitted to hospital each year having sustained injury (3). Rib fractures represent the most common non-spinal fracture in older people (4). Advancing age is a predictor of morbidity and mortality in patients with rib fractures (5). Pain from rib fractures can compromise normal respiratory function, resulting in lung collapse and respiratory compromise. As a result, over 15% of older patients with rib fractures suffer from pulmonary complications, including pneumonia and death (5). Older patients who suffer from pulmonary complications have an increased hospital length of stay, with one study demonstrating a mean increase in length of stay of nine days (6). Interventions to reduce the incidence of pulmonary complications are urgently required to enhance patient care. This feasibility trial will test a novel early intervention in older patients with rib fractures which has the potential of fulfilling this unmet need.

For years the mainstay for treatment of rib fracture pain has been strong opioid analgesia, such as morphine. However, as a result of poor physiological reserve, older patients are vulnerable to the side effects of strong opioid medication such as nausea (14%), constipation (48%), sedation and delirium and respiratory depression (7). Some invasive approaches, such as thoracic epidural anaesthesia, have been used to reduce the likelihood of these side effects, yet such approaches require specialist anaesthetic support and monitoring in a high-dependency environment (8), which may not always be possible in a resource-limited NHS. A meta-analysis found no significant benefit of thoracic epidural analgesia on mortality, admission to intensive care or hospital length of stay in adults with rib fractures (9). In addition, such invasive techniques are unlikely to be available to patients in the first few hours after injury, within the Emergency Department (ED), where opioid analgesia is still the mainstay of treatment.

Local anaesthesia, through paravertebral nerve blockade, has been shown to reduce pulmonary complications in patients with rib fractures when compared to opioid analgesia (10). However, this technique is also invasive. Topical lidocaine patches have been suggested as a non-invasive method of local anaesthetic delivery for use in patients with rib fractures to improve respiratory function, reduce opioid consumption and consequently reduce pulmonary complications (11). Lidocaine patches have been shown to be effective and safe in the treatment of other pain, such as postherpetic neuralgia (shingles) (12). The penetration of lidocaine through the skin is sufficient to produce an analgesic effect but only 3% of the dose applied is expected to be absorbed systemically when used according to the recommended dosing instructions (13). Numerous studies have evaluated safety of the patches and no clinically significant systemic adverse effects have been noted, including when used in an elderly population (13). Given the close proximity of ribs to the skin it is reasonable to suggest that lidocaine from a patch will be absorbed close to the fracture site, although this has only been demonstrated in animal models (14). However, Lidocaine patches are not licensed for use in the treatment of rib fractures, although anecdotally some centres are using them for analgesia in rib fractures. Our 2015 review demonstrated that there is no robust evidence to support the use of lidocaine patches to improve pain control and reduce opioid analgesic use (15). Furthermore, despite sound physiological principles, with improved local pain relief and a potential reduction in strong opioid use, no study to date has evaluated whether lidocaine patches can reduce pulmonary complications.

Only three small studies have evaluated the use of lidocaine patches in patients with rib fractures and none has focussed on older patients who stand to gain most benefit from improved analgesic regimens. One retrospective observational study of 58 adult patients found improvements in subjective pain scores in patients with lidocaine patches applied but no difference in opioid use (16). These results may be biased and lack precision due to low patient numbers, the presence of other injuries and the unblinded methodology used. A single centre double-blind placebo controlled trial, also including 58 patients, showed a trend towards improved pain scores in patients who were given lidocaine patches, but was underpowered to show a statistically significant difference between groups (17). Finally, one small (n=44) prospective double-blind study has evaluated lidocaine patches in patients with isolated rib fractures (18). Although underpowered, this demonstrated a reduction in length of hospital stay and additional opioids used. However, with a median age of 56 years and a failure to capture adverse respiratory events the applicability of these study findings to older patients is limited. No planned studies involving lidocaine patches in rib fractures have been found by searching trial registries.

Limitations on prescribing (only permitted by pain specialists) mean that in centres where lidocaine patches are used, access to them is invariably delayed. In unpublished data from our own institution (North Bristol NHS Trust) lidocaine patches are prescribed on average 3.2 days after injury. This delay may impact upon the effectiveness of the intervention in reducing pulmonary complications, yet early intervention remains untested.

Older patients are under-represented in clinical trials (19), and there are major barriers to recruitment of older adults in research relating to substantial health problems, social and cultural barriers, and potentially impaired capacity to provide informed consent (20).

The need for a feasibility trial

We have identified a number of uncertainties around conducting a trial evaluating lidocaine patches in older patients with chest trauma which necessitate a feasibility trial. These include uncertainties around what outcomes are of greatest importance from a patient perspective, the acceptability of the intervention, length of follow-up required to capture the outcome of pulmonary complications and important potential secondary outcomes such as side effects of opioid medications and the use of aged-based inclusion criteria.

4 AIMS AND OBJECTIVES

4.1 Aim

The aim of this study is to investigate the uncertainties around trial design and conduct to establish whether a definitive trial is feasible and to optimise the design of such a trial.

4.2 Objectives

The objective is to test processes and gather information for the planning of a definitive randomised controlled trial (RCT) to evaluate early topical lidocaine patches in older patients admitted to hospital with rib fractures.

4.3 Feasibility endpoints/outcomes

Feasibility endpoints/outcomes are summarised in ***Table 1***, below. Data collection is also detailed in section 12.

Table 1 Summary of feasibility endpoints/outcomes and measures

Feasibility Outcome	Measure / Tool
A) Number of eligible patients approached.	Screening log (study-specific) records.
B) Proportion of approached patients randomised.	Screening log and randomisation records.
C) Attrition (including both failure to complete the trial protocol and loss to follow up).	Research data and withdrawal records.
D) Proportion of recruited patients for which the primary outcome is available and completeness of each secondary outcome measure.	Research data.
E) Acceptability of the trial processes to clinicians and participants.	Qualitative interviews (see Qualitative section 13).
F) Acceptability of outcome measures to patients.	Qualitative interviews (see Qualitative section 13).
G) Adherence to the intervention.	Inpatient prescribing records.

4.4 Clinical endpoints/outcomes

Clinical endpoints/outcomes are summarised in ***Table 2***, below. Data collection is also detailed in section 12. Clinical endpoints are collected to understand feasibility of data collection to inform a definitive trial and not conduct hypothesis testing.

Table 2 Summary of clinical endpoints/outcomes and measures

Clinical Outcome	Measure / Tool
1) 30-day pulmonary complications.	Patient records: As a single binary composite measure which includes clinical diagnosis of chest infection, pneumonia, pleural effusion or empyema, need for ventilatory support and death secondary to a pulmonary cause if documented in patient records.
2) Incidence of frailty syndromes / analgesia side-effects.	Patient records: As both a single binary composite measure and as binary individual outcomes to include, immobility, delirium, and constipation evaluated during the 72-hour intervention period and functional decline at discharge (discharge destination and support required) (Rockwood Clinical Frailty Scale (21), Timed Up and Go Test (22), The 4-AT (23) and Bristol Stool Chart (24). Development of acute delirium during inpatient stay also at 30-days (single item question).
3) All-cause mortality.	Patient records / electronic patient tracking systems.
4) Intensive Care admission and length of stay.	Patient records / electronic patient tracking systems.
5) Hospital re-admission within 30-days.	Patient records / electronic patient tracking systems.
6) Total length of hospital stay[A].	Patient records / electronic patient tracking systems.
7) Total opioid consumption in first 72-hours of admission.	Patient records.
8) Total pain experienced over the 72-hours period.	Visual Analogue Scale (VAS) (25), and the Abbey pain scale (designed for use in non-verbal patients with dementia) (26).
9) Health economic scoping.	EQ-5D-5L questionnaire (27) at baseline (retrospective pre-injury and post injury) and 30-days. The ICECAP-O (28-30) and Chest Trauma Score (RibPROM[B]) questionnaires at 30-days. Plus, information on key costs such as length of stay, intensive care use and medication prescribing (see Health Economic section 14).

[A] If >30 days actual discharge date will be collected where feasible as this will inform the follow-up period for the definitive trial. Cut-off for this, however, is where participants remain in hospital at the point of follow-up completion for the final participant; length of stay will be recorded as >30 days if appropriate.

[B] The Chest Trauma Score (RibPROM) is a 32-item patient reported outcome measure (PROM) assessing quality of life after rib fracture. The instrument was developed with the assistance of 23 patients who had survived previous chest wall injury. During a series of semi-structured interviews and focus groups, these patients identified significant symptoms and themes that they found important during their recovery. These themes include pain, respiratory health, participation in activities, self-care and psychological health and are reflected in the domains of the PROM. A further content validity study, based on the COSMIN checklist of measurement properties of 6 patients and 9 health professionals, lead to the current version. Local pilot testing in 50 patients with rib fracture has demonstrated initial suitability of the instrument in a real clinical setting. The score is currently undergoing a multi-centre validation (the outcomes after chest trauma score study). (Supplied by Simon Craxford, University of Nottingham).

5 TRIAL DESIGN

5.1 Summary of trial design and setting

A multicentre, parallel group, individually randomised, feasibility RCT with economic scoping and nested qualitative study. The trial will take place across at least three sites in the UK to ensure demographic spread. We will select Major Trauma Centres that are more likely to see the more severe end of the injury spectrum, and Major Trauma Units that may see patients with less severe injuries.

As confirmed by the Medicines and Healthcare products Regulatory Agency (MHRA), this feasibility trial is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) as defined by the EU Directive 2001/20/EC.

5.2 Project timetable and duration of participation

This project (contracting) started 01 January 2020. The project duration is expected to be 39 months, through to 31 March 2023 (subject to change).

One hundred patients will be recruited and randomised (enrolled) over an 18-month period (subject to change). For all participants, individual trial participation will be from the time of written informed consent until 30 days (+10 days) after date of initial ED attendance. A subset of up to 24 participants and 6 people with carer responsibilities (e.g. Personal Consultees, or equivalent legal representatives in Scotland, or other subsequent carers) will be selected, across all sites, through purposive sampling to undertake a detailed telephone or video call interview for the nested qualitative study. This will be completed within 90 days of initial attendance to the ED.

5.3 Blinding and strategies for minimising bias

This is a single blind trial, with only researchers evaluating clinical outcomes being blinded to group allocation. Our Patient Advisory Group (PAG) were concerned that if nursing staff thought a patient had a patch applied, they would not receive the best available alternative therapy. A single blind non-placebo open trial design has therefore been selected for pragmatic reasons to determine whether lidocaine patches have the potential to reduce adverse outcomes. To reduce selection bias, broad inclusion criteria will be applied, and recruitment will be facilitated 24/7. Given this is a RCT, with stratified randomisation, it is anticipated that intervention and control groups will have similar baseline demographics.

5.4 COVID-19 Considerations

Recognising the current COVID-19 pandemic, and the potential for participants to be diagnosed with this predominantly respiratory condition during the trial period, we have made the active decision not to exclude potential participants with suspected/confirmed COVID-19. As this disease becomes endemic within the community it will be important to test our intervention in all potential participants and the pragmatic/feasibility nature of this trial lends itself to doing this.

The majority of hospitals within the UK have also imposed visitor restrictions in light of the ongoing COVID-19 pandemic. To facilitate timely and appropriate recruitment of patients with mild to moderate cognitive impairment who may potentially lack capacity to consent for themselves, we have adapted our approach for seeking remote advice from Consultees (or consent from Welfare Guardians/Attorneys/Nearest Relative in Scotland); see section 8.3 for details. This is an important step to ensure that the study continues to reach this typically under-served population group.

To aid infection control at sites, the default method of obtaining written informed consent from potential participants will be via a study-specific online eConsent Form that is signed electronically by the patient during a consultation. eConsent does *not* need to be followed up with a paper (wet ink) written consent form as an electronic signature constitutes documented informed written consent. Using wipeable devices will reduce the transmission of infection from paper records.

There will be no high-risk aerosolising procedures undertaken as a result of the trial intervention, therefore risks to researchers enrolling participants in this trial will be low and only standard personal protective equipment (e.g. surgical masks, gloves and apron) will be required.

In the event of a “surge” in COVID-19 cases, the trial status will be reviewed with, and follow the advice of, the study Sponsor in discussion with the Chief Investigator (CI).

6 PARTICIPANT SELECTION

The screening and recruitment of patients, delivery of intervention and recording of outcomes will be carried out within participating EDs in the UK. ***Figure 1*** depicts the patient flow (see page 12).

6.1 Inclusion criteria

Potential participants must satisfy the following criteria to be enrolled in this study:

- Older adult patients (age $\geq$ 65 years).
- Presenting to the ED with traumatic rib fracture(s) (including multiple fractures, flail chest and traumatic haemo/pneumothorax even if this requires intercostal chest drainage), confirmed radiologically (by chest X-Ray or CT scan conducted as part of routine care).
- Requiring hospital admission for ongoing care.

6.2 Exclusion criteria

Potential participants who meet any of the following criteria will be excluded from participation:

- Serious distracting trauma to other body regions (adjudicated by the treating clinician): examples include but may not be limited to: traumatic brain injury with cognitive impairment, acute spinal column fracture or spinal cord injury, abdominal and lower limb injuries requiring surgery, unstable pelvic fracture.
- Requirement for intubation and mechanical ventilation either prehospitally or in the ED.
- History of allergy to lidocaine.
- Open wounds at the site of patch application.
- End-stage dementia (adjudicated by the treating clinician, e.g. bed-bound and non-verbal); patients with mild to moderate cognitive impairment can be approached (see section 8.3 for more details).
- End-stage liver failure with jaundice.
- End-stage heart failure with breathlessness at rest prior to injury.
- Those unable to communicate in English language where all reasonable attempts to source translation services are exhausted within the ED.
- Patients transferred from non-recruiting units to a recruiting site who have a lidocaine patch applied as part of standard care prior to arrival in the recruiting site.

6.3 Co-enrolment to other studies

The CI will ensure appropriate co-enrolment agreements are in place for all studies/trials where similar inclusion criteria are applied. These agreements will consider participant burden and where appropriate, will not be applied where randomised interventions are applied in the ED. In the event of overlapping randomised interventions, it will be at the discretion of the local Principal Investigators (PIs) as to which trial a patient should be approached for potential participation.

7 CLINICAL PROCEDURES

Study participants will have undergone the standard clinical assessment and treatment of patients with suspected rib fractures in the ED. This includes a triage history assessment, routine initial observations of pulse, blood pressure, respiratory rate, and oxygen saturations.

7.1 Pain control

Prior to study screening, study participants will be offered standard analgesia according to local practice by clinical staff. This practice will not be altered for study purposes. Data on analgesia provision prior to study screening, in participating patients, will be collected retrospectively via medical notes to ensure no differences exist between groups.

7.2 Imaging

Imaging to identify the presence of rib fractures will be entirely at the discretion of the treating clinician and not altered for study purposes. Appropriate imaging modalities to identify the presence of rib fractures will include chest X-Ray and CT scan, these will not be performed outside of standard care. For the purpose of this feasibility study, we will assess image transfer from participating sites and consider central review of anonymised images in order to independently evaluate rib fracture patterns should this be required in the main trial.

7.3 Patients transferred from other units

Given some recruiting sites will be Major Trauma Centres, a small proportion of eligible patients may be transferred from other units (e.g. Major Trauma Units, District General Hospitals, Minor Injuries Units), that are not recruiting sites. Patients transferred from other units who have not had a lidocaine patch applied prior to arrival in a recruiting site, may be approached for recruitment. In the unlikely event that a patient is transferred to a recruiting site from another unit and a lidocaine patch has already been applied, as part of standard care, the patient will not be enrolled in the trial but screening data will be collected (see exclusion criteria, above).

8 RECRUITMENT AND CONSENT

Recruitment will be undertaken 24 hours a day, 7 days a week. Recruitment by appropriately trained ED clinicians out of normal research nursing hours will be important to assess as part of this feasibility trial. Potentially eligible participants will be identified at the time of arrival in ED by clinical staff or research nurses. During triage or initial assessment, a member of the ED clinical team or research nurse will give the patient the written study Summary Participant Information Sheet (Summary PIS) and, where appropriate, the full Participant Information Pack (e.g. the patient has read the Summary PIS and requested further information and/or is suitably comfortable and able to read both documents at that time). In some patients, this might be before imaging confirming the presence of rib fractures has been undertaken, so a number of patients who receive the PIS (and full Participant Information Pack) may subsequently be ineligible to enter the study. To ensure equipoise, given that lidocaine patches are in clinical use by specialist pain services in some centres, patients will be recruited when identified in the ED and prior to onward referral to the pain team. The length of time patients will have to consider participation will vary due to the nature of EDs and assessment pathways, however it is estimated to be from 1 to 4 hours; this approach is considered acceptable by patients, as demonstrated by our PAG and other ED-based research undertaken by our group (31).

An approved study-specific poster may also be displayed in suitable clinical areas within the ED, which provides the contact details of trial related staff who interested patients can contact for further information. Site staff should then proceed as described in this section.

Patients who are willing and eligible to participate in the study will be asked to provide written informed consent and they will be allocated a unique study identification (I.D) number. Written informed consent will not be sought until the patient is comfortable and immediate care needs have been addressed. However, given the intervention is early (applied within the ED), consent will be obtained prior to transfer to the inpatient ward. Ideally patients will have read both the Summary PIS and Participant Information Pack before providing written informed consent. We recognise, however, that it may not be appropriate or feasible for some patients (e.g. due to being in pain, frailty, visual impairment) to read both documents, or at least not the Information Pack in full, prior to providing written informed consent. In these circumstances, patients who have read (or discussed) the Summary PIS and are willing and eligible to participate will be asked to provide full (written) informed consent, as outlined below, and will be asked to read (or discuss) the Information Pack in full as soon as appropriate. Informed consent will remain unless the individual requests to change permissions/withdraw, in which case the relevant procedures will be followed; see section 17, Participant Withdrawal.

The written informed consent process will be undertaken by an appropriately trained attending clinician or an appropriate member of the research team depending on individual circumstances. All members of the clinical and/or research team delegated by the PI to undertake the consent procedure must be listed on the study delegation log at the relevant site. Besides completing the consent form (which includes the study title and date of consent), sites should record key details of the informed consent process in the patient's medical notes. Patients are not required to provide reasons for taking part in the study, or not, but if reasons are given, then they should also be documented in their notes.

Randomisation, to inform the treating clinicians which analgesic strategy to follow, can *only* take place once (written) informed consent is obtained (as detailed in section 9).

8.1 eConsent Form (default method)

The default method of obtaining written informed consent will be via a study-approved online eConsent Form (via a REDCap database system and process) that is signed electronically by the patient during a consultation. eConsent does *not* need to be followed up with a paper (wet ink) written consent form as an electronic signature constitutes documented informed written consent.

Five copies (paper print out and/or electronic) of the completed consent form are required. A copy should be: (1) provided to the patient; (2) filed with a copy of the Summary PIS and Information Pack in the participant's ED records; (3) filed in the investigator site file (ISF); (4) provided to the central trial team (University of Bristol study office); and (5) provided to the patient's General Practitioner (GP; see section 9).

When an eConsent Form is completed and processed, a copy will be automatically emailed via the database system to the patient *if* they choose this method and provide an email address. Additional copies can be obtained via the eConsent database system; these should be provided/filed (as required) at the earliest opportunity. We acknowledge that if a participant does not request an automatic email, and/or they are discharged from hospital before a printed copy is available, then a research nurse (or delegate) will send a copy to the participant (e.g. by post).

8.2 Paper (wet ink) Consent Form

If eConsent is not feasible, then a paper (wet ink) equivalent Consent Form should be completed and signed by the patient and countersigned by the staff member taking consent. As noted above, five copies of the completed consent form are required; when a paper (wet ink) consent form is completed, the 'original' form should be filed in the ISF. The research nurse (or delegate) will provide/file additional copies as required.

NB: When a patient has capacity but is unable to indicate their consent by signing/marking a Consent Form (paper or electronic version); then they may give their informed consent verbally in the presence of a witness (any clinician on duty, nurse or doctor) *in addition to* the staff member taking consent. The witness will also be asked to countersign the consent form.

8.3 Patients with mild to moderate cognitive impairment who may potentially lack capacity to provide consent for themselves

We feel it is important to include those patients with mild to moderate cognitive impairment. We acknowledge that a patient's cognitive impairment may relate to a neurodegenerative disease, such as dementia, which is likely to remain throughout the duration of the trial due to its chronicity. One third of patients aged over 65-years admitted to hospital after a fall have dementia (32). Patients with dementia are more susceptible to both the effects of pain after injury and to the side effects of strong opioid medication traditionally used to treat rib fractures (33). There is an increasing recognition that older patients will under-report pain, however, studies evaluating this important issue have failed to address cognitive impairment as a confounder in pain reporting (34). Alternatively, a patient's cognitive impairment may be due to an acute medical condition or emergency, such as delirium, and may therefore be temporary.

As such, it is important to test lidocaine patches in these vulnerable groups and gain further understanding in pain reporting in patients with mild to moderate cognitive impairment. However, these patients may lack capacity to provide consent for themselves if they are unable to:

- understand the information relevant to the decision
- retain the information
- use or weigh the information
- communicate their decision (by any means).

All senior ED clinicians and research nurses have training in capacity assessment. If a potential participant is identified as lacking capacity to provide consent for themselves at the time a decision or action needs to be taken, then trained research or Good Clinical Practice (GCP) trained clinical staff will take reasonable steps to seek an opinion as to whether the patient would wish to participate if they had capacity. See sections 8.3.1 and 8.3.2 below for further details, including reference to patients who may regain capacity during the 30-day trial period.

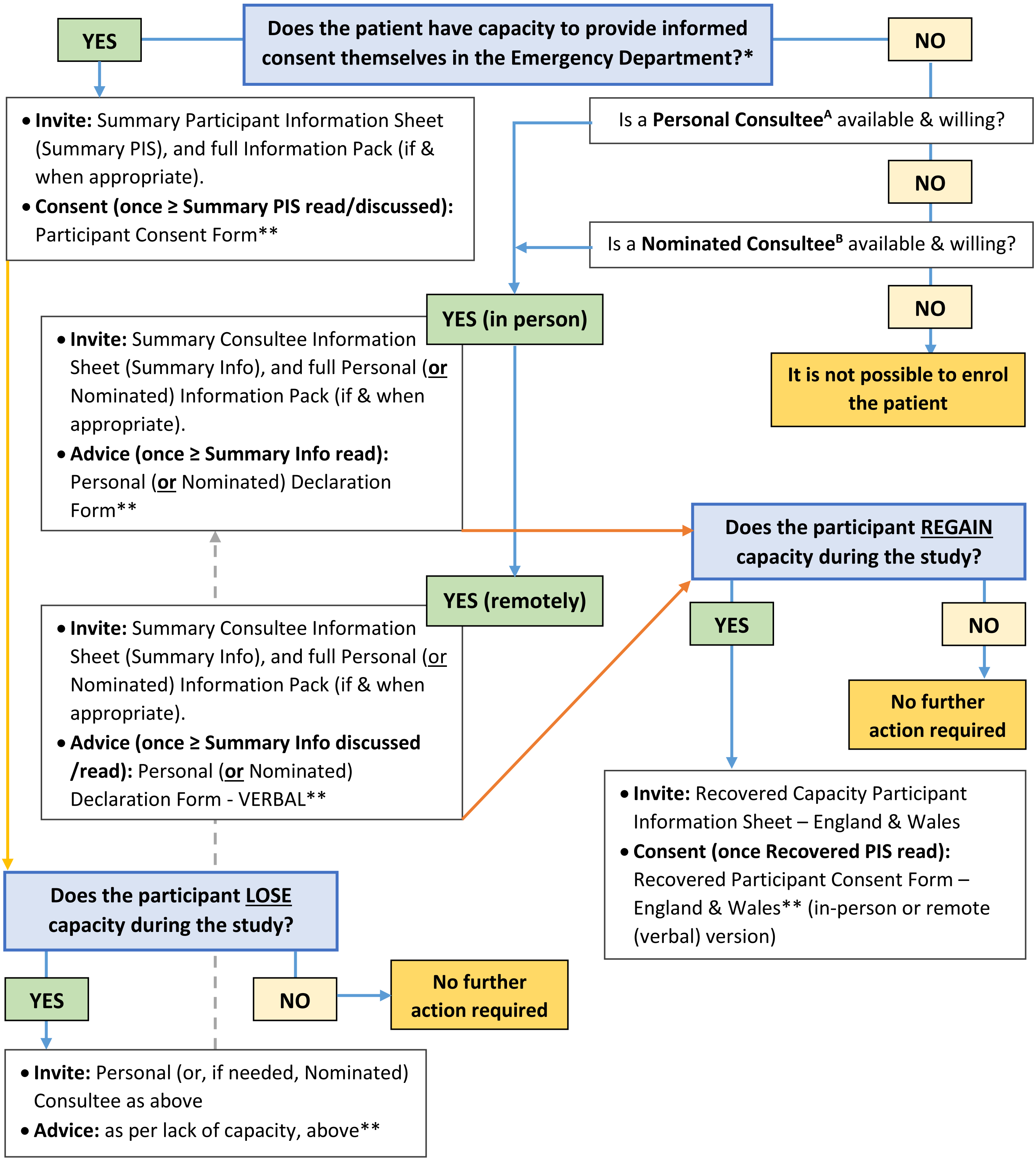
For participants who have capacity at the time of consent in the ED, but who later lose capacity during the trial (e.g. due to developing acute delirium), see section 8.4.

A summary of the various study invitation and consent pathways, as detailed throughout this section of the protocol, are shown in

***Figure* 2 (patients in England and Wales) and**

Figure 3 (patients in Scotland), below. Appendix 1 also presents an equivalent table.

The acceptability of the consent process with patients, Personal Consultees with carer responsibilities (or equivalent Welfare Guardians or Attorneys/Nearest Relatives in Scotland), and clinicians will be explored (integrated qualitative study), in order to inform the consent processes of a full trial; see section 14 for further details.



Notes:

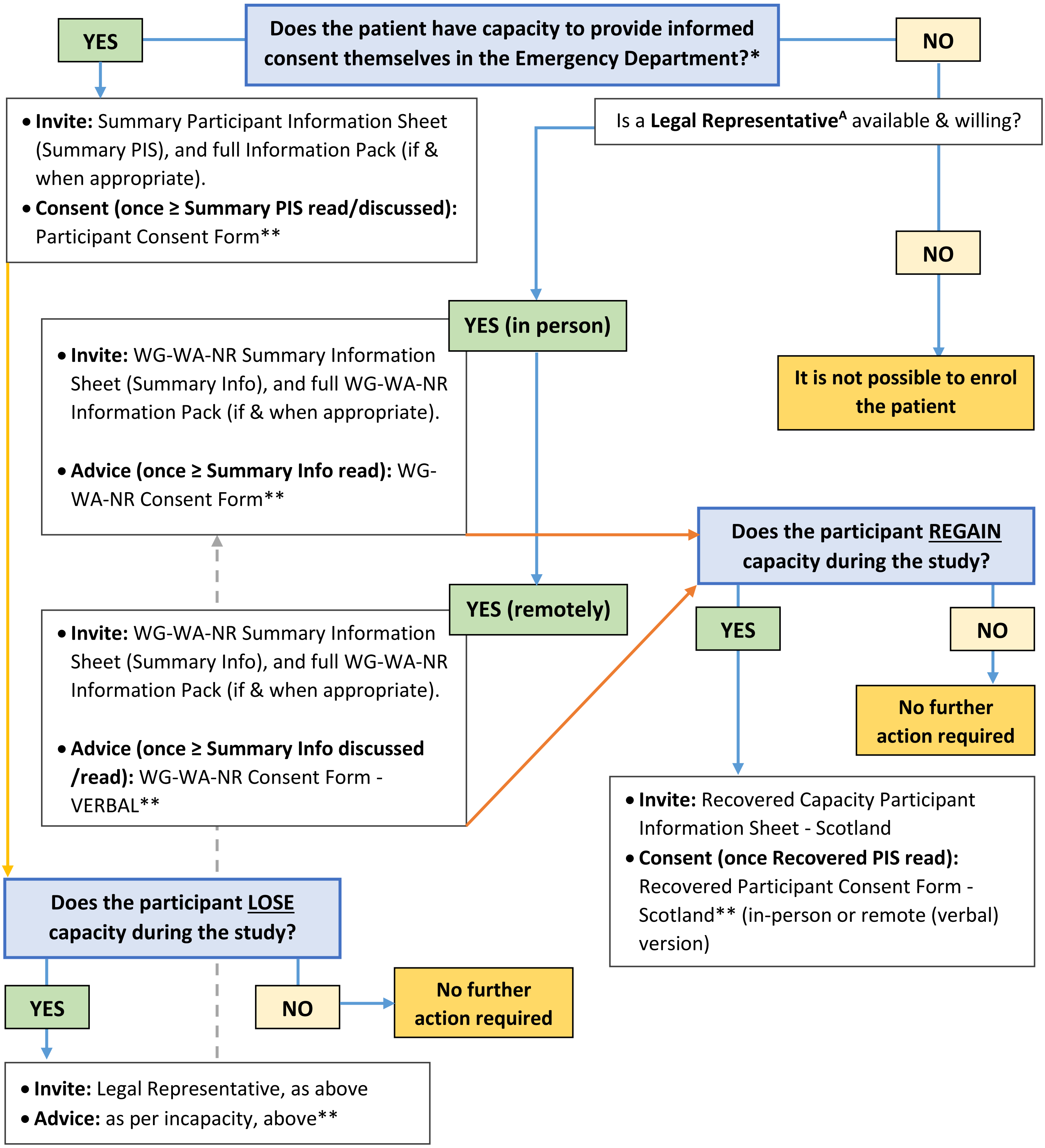
*The study invitation and consent process presented here is in line with the Mental Capacity Act 2005 for patients in England and Wales.

The default method of completion is via the appropriate online eConsent (or eDeclaration) Form. If the online form is not feasible, then a paper version is available. Site Staff should update the **RELIEF Screening Log at all relevant timepoints.

[A]The patient's partner, or a particular friend or carer who is not seeking renumeration for doing so or acting in a professional capacity.

[B]Nominated Consultee is someone at the participating site appointed by the local PI. This may include a member of the care team as long as they are not connected with the project to avoid potential conflict; the CI and locals PIs are therefore excluded.

Figure 2 Participant information and consent pathways for patients in England and Wales*



Notes:

*The study invitation and consent process presented here is in line with the Adults with Incapacity (Scotland) Act 2000 for patients in Scotland.

The default method of completion is via the appropriate online eConsent (or eDeclaration) Form. If the online form is not feasible, then a paper version is available. Site Staff should update the **RELIEF Screening Log at all relevant timepoints.

[A]A Welfare Guardian (WG) or Welfare Attorney (WA), or if not in place then the patient's nearest relative (NR).

Figure 3 Participant information and consent pathways for patients in Scotland*

8.3.1 England and Wales (Mental Capacity Act 2005)

A) Initial enrolment to the trial

If a potential participant in England and Wales is identified as lacking capacity to provide consent for themselves at the time a decision or action needs to be taken, clinical staff will take reasonable steps to seek an opinion from a Personal Consultee (e.g. their partner, or a particular friend or carer who is not seeking renumeration for doing so or acting in a professional capacity), as per the Mental Capacity Act 2005.

The majority of hospitals within the UK have imposed visitor restrictions in light of the (ongoing) COVID-19 pandemic. In order to facilitate timely and appropriate participant recruitment with Personal Consultee approval, discussion of the trial will be made via telephone (or alternative method if requested by the Consultee and where it is appropriate and feasible, e.g. Sponsor/NHS-approved video/tele-conference platforms) in the first instance with a Consultee Summary Information Sheet, and where feasible and appropriate, the further Personal Consultee Information Pack; both documents will be made available through the study website to view and download by the Consultee, or sent by email if required.

Ideally the Consultee will have discussed (and/or read) both the Consultee Summary Information Sheet and appropriate Consultee Information Pack before providing informed advice. We recognise, however, that it may not be appropriate or feasible for some Consultees (e.g. due to limited time) to discuss (read) both documents, or at least not the Information Pack in full, prior to providing informed advice. In these circumstances, Consultees who have at least discussed (or read where feasible) the Consultee Summary Information Sheet will be asked to provide full written informed advice, as outlined below, and asked to read the Information Pack in full as soon as appropriate. Informed advice will remain unless the individual requests to change permissions/withdraw, in which case the relevant procedures will be followed; see section 17, Participant Withdrawal.

Advice from a Consultee about whether the named patient would wish to be included in the trial or not, can be obtained via telephone (or alternative method as noted above) by completing the appropriate “Verbal” Consultee Declaration Form with a member of the research team. The Declaration Form will capture that the Consultee confirms they have at least discussed the study information, had the opportunity to ask any questions, and gives their advice. Similar to section 8.1, the default method of recording the Consultee’s advice will be via an appropriate online eDeclaration Form. If the appropriate eDeclaration Form is not feasible, then a paper (wet ink) equivalent will be available.

Five copies of the completed Declaration Form are required. A copy should be: (1) provided to the Consultee with a copy of the information sheets (summary and full information pack) (e.g. via email or post, as they prefer); (2) filed with a copy of the information sheets in the participant’s ED records; (3) filed in the ISF; (4) provided to the central trial team (study office); and (5) provided to the patient’s General Practitioner (GP; see section 9).

If the Personal Consultee is present, then information can be provided in person and advice obtained by completing the appropriate “In-Person” Consultee (e)Declaration Form. As noted above, five copies of the completed form are required.

Where appropriate, and if requested by the Personal Consultee, the research team will invite collaboration in the completion of any questionnaires or research procedures. The ability of participants with mild to moderate cognitive impairment to complete study related questionnaires is an important feasibility outcome in terms of completeness of data.

If someone declines the invitation to be a Consultee, they will not be asked to sign anything, however the clinical (research) team will record, in the relevant study documentation and patient records, that that person was asked and said no; this is so that they are not asked again about this role in the future.

If reasonable steps to contact a Personal Consultee have failed (e.g. where no family member or friend is willing and able to act as consultee, or where the family or friend live a long distance away, and/or are unable to at least discuss the information sheet(s) within adequate time), and/or a Personal Consultee becomes unavailable during the study, or is no longer willing to undertake the role, then a Nominated Consultee will be approached to advise the researcher about the participation of the person who lacks capacity. The Nominated Consultee will be provided with the Consultee Information Summary Sheet, a Nominated Information Pack, and appropriate (e)Declaration Form; agreement will be sought in the same way as noted above, for the Personal Consultee. For the purposes of this trial a Nominated Consultee will be someone at the participating site (hospital) who is appointed by the local PI. This may include a member of the care team as long as they are not connected with the project to avoid potential conflict; the CI and locals PIs are therefore excluded.

If the Personal or Nominated Consultee advises the research team that the participant should be withdrawn from the study, the research team must withdraw them.

B) If a patient (participant) regains capacity during the 30-day trial period

If a patient (participant) regains capacity to consent during their 30-day trial period, then suitable clinical/research staff will ask them to give their own retrospective consent when and if they are able. Such patients will be provided with the appropriate “Recovered Capacity Participant Information Sheet and Recovered Capacity (e)Consent Form”, that explains what has happened so far and what we are seeking their consent for. Where feasible, the patient will not be informed about their treatment allocation group, nor will any further trial assessments and/or procedures take place until after retrospective consent has been obtained. If the patient advises that they no longer want to take part in the study the patient will be withdrawn; see section 17 (Participant Withdrawal). Consultees will be informed of this retrospective consent process at the outset via the Consultee study information materials. As per sections 8.1 and 8.2, the default method of recording the patient’s “recovered consent” will be via the appropriate online eConsent Form. If eConsent is not feasible, then a paper (wet ink) equivalent will be available (or verbal equivalent if obtaining via telephone, or alternative method of remote contact). Five copies of the completed consent form are required. A copy should be: (1) provided to the participant with a copy of the information sheet; (2) filed with a copy of the information sheet in the participant’s ED records; (3) filed in the ISF; (4) provided to the central trial team (study office); and (5) provided to the patient’s GP with the appropriate study approved letter (which should also be filed in the ISF).

8.3.2 Scotland (Adults with Incapacity (Scotland) Act 2000)

A) Initial enrolment to the trial

If a potential participant in Scotland is identified as lacking capacity to provide consent for themselves at the time a decision or action needs to be taken, clinical staff will take reasonable steps to recruit adults lacking capacity to consent for themselves, as per the Adults with Incapacity (Scotland) Act 2000. Where feasible, consent will be obtained on behalf of the patient who lacks the capacity to do so themselves, from a legal representative (i.e. a Welfare Guardian or Attorney, or from the patient's nearest relative if a Welfare Guardian or Attorney is not in place). Similar to section 8.3.1 above, discussion of the trial will be made via telephone (or alternative method if requested by the legal representative and where it is appropriate and feasible, e.g. Sponsor/NHS-approved video/tele-conference platforms) in the first instance with a Welfare Guardian or Attorney/Nearest Relative Summary Information Sheet, and, where feasible and appropriate, the further Information Pack; both documents will be made available through the study website to view and download, or sent by email if required.

Ideally the legal representative will have discussed (and/or read) both the Guardian/Attorney/Nearest Relative Summary Information Sheet and appropriate Information Pack before providing informed agreement (consent). We recognise, however, that it may not be appropriate or feasible for some legal representatives (e.g. due to limited time) to discuss (read) both documents, or at least not the Information Pack in full, prior to providing informed consent. In these circumstances, those who have at least discussed (or read where feasible) the appropriate Summary Information Sheet will be asked to provide full informed consent, as outlined below, and asked to read the Information Pack in full as soon as appropriate. Informed consent will remain unless the individual requests to change permissions/withdraw, in which case the relevant procedures will be followed; see section 17, Participant Withdrawal.

Agreement (written consent) can be obtained by completing an appropriate Welfare Guardian or Attorney/Nearest Relative "Verbal" Consent Form, to confirm they have at least discussed the study information, had the opportunity to ask any questions, and give their consent on behalf of the patient who lacks the capacity to do so for themselves. Similar to above, the default method of recording the consent will be via the appropriate online eConsent Form. If eConsent is not feasible, then a paper (wet ink) equivalent will be available.

Five copies of the completed form are required. A copy should be: (1) provided to the legal representative with a copy of the information sheets (summary and full information pack) (e.g. via email or post, as they prefer); (2) filed with a copy of the information sheets in the participant's ED records; (3) filed in the ISF; (4) provided to the central trial team (study office); and (5) provided to the patient's GP (see section 9).

If the legal representative is present, then information can be provided in person and consent obtained by completing an "In-Person" (e)Consent Form. As noted above, five copies of the completed form are required.

If the legal representative advises the research team that the participant should be withdrawn from the study, the research team must withdraw them.

If someone declines the invitation to provide consent on behalf of the patient who lacks capacity to do so for themselves, they will not be asked to sign anything, however the clinical (research) team will record, in the relevant study documentation and patient records, that that person was asked and said no; this is so that they are not asked again about this role in the future.

In Scotland, there are currently no provisions for non-CTIMP trials if reasonable steps to contact a legal representative, such as a Welfare Guardian or Attorney/Nearest Relative, have failed (e.g. where no one is willing and able to act on behalf of the patient, or where they live a long distance away and/or are unable to discuss (read) the information sheet(s) within adequate time). In such cases, these patients will not be recruited into this trial. This should be recorded on the screening log to inform the design of a full trial (see section 8.5, below).

B) If a patient (participant) regains capacity during the 30-day trial period

The same approach identified in section 8.3.1-B above will be utilised. Noting, however, that the appropriate legal representative (rather than Consultee) will be informed of this at the outset, via the study information materials they were originally provided.

8.4 Participants who lose capacity during the 30-day trial period

For participants who have capacity at the time of consent in the ED, but who later lose capacity during their 30-day trial period (e.g. due to developing acute delirium), the following processes' will apply.

8.4.1 England and Wales (Mental Capacity Act 2005)

If a participant in England and Wales loses capacity during their 30-day trial period, then their consent obtained prior to loss of capacity will not endure the loss. As soon as feasible following confirmed loss of capacity, an appropriate member of the clinical and/or research team will approach either a Personal (or, if not available, a Nominated) Consultee about the patients' continuing participation in the trial, according to the provisions of the Mental Capacity Act 2005.

If a Consultee is not available or is unwilling, or advises that the participant should no longer take part in the trial after they have lost capacity, then the participant will be withdrawn but data already collected up to the point of loss of capacity will be retained; see section 17 (Participant Withdrawal).

Advice from a Consultee about whether the named patient would wish to be included in the trial or not, will be obtained in the same way described in section 8.3.1-A, above. Patients will be informed of this process at the outset via the participant study information materials they were originally provided.

8.4.2 Scotland (Adults with Incapacity (Scotland) Act 2000)

In Scotland, there is no legal, specified provision for adults who lose capacity while taking part in a non-CTIMP study, thus the Adults with Incapacity (Scotland) 2000 act does not apply. If a participant in Scotland, therefore, loses capacity during their 30-day trial period, then we will utilise an approach similar to that for participants in England and Wales. That is, as soon as feasible following confirmed loss of capacity, an appropriate member of the clinical and/or research team will approach a legal representative about the patients' continuing participation in the trial.

If a legal representative is not available or is unwilling, or advises that the participant should no longer take part in the trial after they have lost capacity, then the participant will be withdrawn but data already collected up to the point of loss of capacity will be retained; see section 17 (Participant Withdrawal).

Consent from a legal representative will be obtained in the same way described in section 8.3.2–A, above. Patients will be informed of this process at the outset via the participant study information materials they were originally provided.

A summary of the various study invitation and consent pathways, as detailed throughout this section of the protocol, are shown in

***Figure* 2 (patients in England and Wales) and**

Figure 3 (patients in Scotland), above. Appendix 1 also presents an equivalent table.

8.5 Screening logs

Hospital staff will complete a trial-specific screening log, which will be developed in line with the SEAR (Screened, Eligible, Approached, Randomised) framework (35); this framework will enable us to record the flow of potential participants through the recruitment process, in line with recommended Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines (36, 37). Where possible, screening logs will include reason(s) for non-participation.

Given the setting of this trial (i.e. the ED, 24 hours a day, 7 days a week), it is acknowledged that completion of screening logs may not be feasible at all times. Thus, a pragmatic approach to screening logs will be taken and trial-specific guidance will be provided to participating sites.

Sites will provide the central trial team (study office) with a copy of their screening logs on a regular basis (e.g. monthly), for monitoring purposes.

9 RANDOMISATION

Immediately after diagnosis in the ED, and after informed consent has been obtained, participants will be randomised on a 1:1 ratio to either the lidocaine patch (intervention) or standard care (control) group. An online randomisation system will be used, with the randomisation sequence being generated by the company "Sealed Envelope™" (38). Randomisation will be stratified by both study site and gender as a dichotomous variable and blocked within strata.

Appropriate staff at all sites, as delegated by the PI, will be provided with log-in details for the secure online randomisation system, and study database where applicable.

To randomise a participant, the recruiting doctor or appropriate site staff will sign into the online randomisation system and enter brief participant details (e.g. unique study I.D. number, study site, gender, date of birth and date of informed consent (advice)). Once the online randomisation process is complete, the computer screen will indicate to treating clinicians which analgesic strategy to follow. Site staff will place a relevant pre-prepared 'treatment allocation group' sticker in the patient's ED records (where feasible). "Sealed Envelope™" will automatically send an email to relevant users that have 'notifications enabled' confirming the randomisation. Appropriate site staff will place a record (electronic or print out) of the allocation generated by the randomisation website in the participant's ED notes and ISF.

Once a participant has been randomised, they are enrolled in the study and treatment (intervention delivery) can proceed. Hospital (site/equivalent research) staff should proceed to complete and send a study approved letter to the participant's GP, including a copy of their patient's completed consent form (or declaration form where appropriate), informing them that their patient has entered the trial; a copy of this letter should also be filed in the ISF.

10 TRIAL STRATEGIES

Patients will be randomised on a 1:1 ratio to either the lidocaine patch (intervention) or standard care (control) group immediately after diagnosis in the ED and written consent is obtained.

10.1 Intervention

Patients randomised to the intervention group will have up to 3 x 700mg lidocaine patch(es) (Ralvo®) applied over the most painful area of rib injury after first diagnosis as soon as practical within the ED. The patches will be applied once daily for 12 hours in accordance with the manufacturer's (Grünenthal) instructions, followed by a 12-hour patch-free period. Treatment will continue for up to 72 hours or until the time of discharge, whichever is sooner. The intervention is additive to standard clinical management (described below).

10.2 Control (standard clinical management)

All patients regardless of randomised treatment allocation will receive standardised treatment according to local analgesic guidelines for patients with rib fractures. This should include prescription of regular paracetamol, ibuprofen (unless contraindicated) and codeine phosphate (or alternative weak opioid). Adherence to prescribing according to local guidelines will be recorded and any reasons for non-adherence will be recorded. It is anticipated that some participants may require stronger opioid analgesia, such as oral morphine. Given a secondary clinical outcome measure of morphine use over 72 hours is included, opioid prescription will not be controlled and will be analysed for potential differences between groups. Some recruited participants will also undergo regional anaesthesia such as thoracic epidural or nerve block. There is currently no accepted standard for these types of advanced intervention and consequently provision and technique will vary between centres. We will therefore be unable to control regional anaesthesia provision across the study population. We also recognise that provision of regional anaesthesia may vary between intervention and control groups and these data will be collected to inform selection of different centres for the main trial. Should regional anaesthesia be deemed necessary by the treating clinician, patches will be removed, no further patches will be applied, and group allocation maintained. To ensure equipoise, given that lidocaine patches are in clinical use by specialist pain services in some centres, patients will be recruited when identified in the ED and prior to onward referral to the pain team.

10.3 Cross-over of intervention arms

Given lidocaine patches may be prescribed by inpatient teams (acute pain services) in some study sites, some patients allocated to the control strategy may receive lidocaine patches during their inpatient stay. Our audit data suggest this is unlikely to occur in the initial 24 hours after injury. Given this is routine clinical practice inpatient prescribing practices will not be controlled. Sites will be asked to monitor and record all treatments that a participant receives; if cross-over does occur then details, including reason(s) why should be recorded in study case report forms (CRFs). If significant cross-over does occur this may inform alterations in the design of the definitive trial e.g. the use of placebo patches.

11 LIDOCAINE PATCH SUPPLY, STORAGE AND PRESCRIPTION

11.1 Supply

Trial medication will be obtained from normal local hospital pharmacy supplies, ordered and received in accordance with Pharmacy standard operating procedures (SOPs). Sites will pre-order boxes from local pharmacy prior to study commencement. Each box contains 6 envelopes of 5 x lidocaine patches.

Medication issued for use in the trial will be supplied in the original manufacturer's packaging. 700mg lidocaine patches are supplied in envelopes containing 5 x patches. One pack should be sufficient for each patient enrolled into the intervention arm for the duration of the trial. In the event of spoilage or patient need for additional patches (e.g. bilateral rib fractures or large painful surface area), additional patches will be obtained from normal local hospital pharmacy supplies. The lidocaine patch manufacturer's (Grünenthal) packaging will not be altered for trial purposes. At the point of randomisation, each pack of 5 x patches (and additional patches if required) will be placed by a delegated member of the ED research team, for the duration of the intervention (72 hours), in a bespoke paper study envelope, which will be labelled with the participants name, NHS number and unique study number. This envelope will be destroyed in secure confidential waste after the intervention has been completed.

Accurate records for medication dispensed and returned must be maintained and a record available for inspection.

11.2 Storage

Lidocaine patches contained within labelled bespoke study envelopes will be stored in locked dry storage cabinets within the ED marked "For Research Use Only" (or similar). Storage will be at room temperature and temperature monitoring will not be required.

11.3 Prescription

Prescription of lidocaine patches in the intervention arm will be pre-printed on a trial-specific sticker which can be inserted onto a standard hospital drug chart or on hospital ePrescribing systems (where in use). The sticker will include clear instructions around the 12-hour prescription of each 700mg lidocaine patch followed by a 12-hour patch free period for a total duration of 72-hours and signed by a registered medical practitioner or prescribing nurse. Up to 3 x 700mg patches can be applied at one time in the event of bilateral rib fractures or a large painful surface area (as per British National Formulary, https://bnf.nice.org.uk/).

11.4 Cautions

We recognise that caution should be applied in the use of lidocaine patches for some patients (as per British National Formulary). Of relevance to our study population, these cautions include severe renal impairment, hepatic impairment, and congestive cardiac failure. Given the pragmatic nature of this trial and to reflect routine prescribing practices we have excluded patients with end-stage liver failure with jaundice and end-stage heart failure with breathlessness at rest prior to injury. Patients with severe renal failure may still be recruited but routine monitoring for adverse effects will be undertaken.

Adverse effects of medications will be considered in event monitoring (see section 15 for further details) and local adverse incident reporting for clinical events will follow routine local practice, e.g. DATIX at the discretion of the local PI.

11.5 Return/destruction of trial medication

Sealed and unused lidocaine patch envelopes can be returned to pharmacy and considered for re-use according to local policies. Return of unused medication should be logged by local pharmacies.

Used lidocaine patches and opened envelopes should be disposed of according to local best practice.

Table 3 Schedule of trial assessments and key participant-related procedures

Data collection timepoint (→) Data capture / key trial procedure (↓)	In the Emergency Department (ED)		Post-Randomisation Follow Ups		
	Recruitment	Post-Recruitment (Baseline)	72-hours (3-days) Intervention Period	30-days (+10 days)	Up to 90-days
Screening, Consent & Randomisation	X				
Case Report Forms (CRFs: study-specific)		X	X	X	
Observations and Injury data*[A]		X			
Rockwood Frailty Scale*		X			
EQ-5D-5L (retrospective pre-injury, and post injury at Baseline)		X		X [B]	
Immobility: Timed Up and Go Test		X	X		
Intervention delivery		←	→		
Total opioid consumption (first 72 hours)*			X		
Pain: 4-hourly VAS and Abbey Pain Scores (during first 72 hours)		←	→		
Delirium: Daily 4-AT during 72-hour intervention period. Single item question at 30-days.		←	→	X	
Opioid Induced Constipation (notes screen for Bristol Stool Chart)*			X		
Pulmonary complications (notes screen) and Intensive Care Unit admission*				X	
Mortality (notes screen)*				X	
Hospital Re-admission (GP records/notes screen)*				X	
Length of Stay*				X	
Discharge destination and support required*				X	
Chest Trauma Score (RibPROM)				X [B]	
ICECAP-O Quality of Life				X [B]	
Qualitative interviews (see section 13) [C]		←			→

** These data are routinely collected in the NHS, thus are not collected specifically for the purpose of this trial. Data will be taken from medical records and recorded in the CRF(s).*

[A] Injury Severity Score (ISS) may be calculated retrospectively after validation by the Trauma and Audit Research Network.

[B] Face-to-face (or online) data collection if still inpatient, or via post/telephone/online if not (+10 days allowance). For further details, see section 12, Data Collection.

[C] Qualitative interviews with patients (participants) and people with carer responsibilities (e.g. Personal Consultees, or equivalents in Scotland, or other subsequent carers) will take place, noting that timing is flexible from baseline and up to 90 days after initial ED attendance (randomisation).

12 DATA COLLECTION

Data collection will focus upon feasibility outcomes as detailed in section 4, above. Demographic and clinical data will be recorded after randomisation by the treating clinician or member of the study team. Data will be collected face-to-face (where the participant is still an inpatient, or via telephone, post and/or online if not) or from patient records using data routinely collected in the NHS. Data will be recorded into paper (and/or online) questionnaires and CRFs and either entered at site by delegated clinical/research site staff into a trial specific database, or sent securely (electronically or by post) to the central trial team (study office) for entry into the trial specific database. See section 19 for further details about data management.

12.1 Schedule of assessments and outcome data collection

Table 3 (previous page) depicts the key assessments/outcome measures and participant-related procedures scheduled at various trial timepoints. Further details are provided in this section, below.

To summarise, participants in the trial will undergo:

- Screening, Consent and Randomisation
- Assessments and data collection at baseline
- Treatment (intervention) delivery at baseline for up to 72-hours (3-days)
- Assessments and data collection during (and at) the first 72-hours (3-days) post-randomisation
- Follow up at 30-days (+10-days) post-randomisation.

For all outcome assessments, participants and delegated clinical and research staff at the participating sites will not be blinded to the participant's treatment allocation, as outlined in section 5.3.

NB: One of the five statutory principles of the Mental Capacity Act 2005 is that "a person must be assumed to have capacity unless it is established that they lack capacity" (39). Thus, where a participant has consented to take part, it is reasonable to assume that capacity remains. Throughout the trial, however, the researcher should be vigilant to any changes indicating that capacity has been lost (e.g. by monitoring the patient where feasible and/or at least checking medical records). Similarly, the researcher should be vigilant to changes to capacity in participants who lacked capacity when joining the study. If changes to capacity are confirmed, the researcher will review the participant's agreement (consent) to take part in the trial and update it accordingly, as detailed in section 8 (Recruitment and Consent).

12.2 Baseline data

Baseline data collection will be conducted after the patient has provided written informed consent and randomisation has taken place.

Questionnaire (participants): Participants will be asked to complete the Baseline study questionnaire (via paper copy or online) which contains (at least) the following patient reported outcome measure (PROM):

- EQ-5D-5L (27) to capture both retrospective pre-injury and baseline post injury (to inform health economics feasibility; see section 14)

CRF (site staff): A research nurse, or other delegated site staff member, will complete the Baseline CRF. CRF contents are derived from outcome measures and demographic information to include (as a minimum):

- Patient contact details
- NHS/CHI number
- Patient demographics, including date of birth and gender
- GP contact details
- Details of Personal and/or Nominated Consultee, or equivalent legal representatives in Scotland (if relevant, including those who decline an invitation to be a Consultee (or provide consent on the patient's behalf, in Scotland))
- Details about usual residence (e.g. own home, residential/nursing home)
- History of lung disease
- History of tobacco smoking
- Mechanism of injury
- Observations on arrival in the ED
- Number of ribs fractures
- Injury Severity Score (ISS) (40). The ISS may be calculated retrospectively after validation on the Trauma Audit Research Network Database.
- To characterise frailty within the study population the Rockwood Clinical Frailty Scale (21) will be recorded at admission, as adjudicated by the treating clinician and information gathered on pre-injury support required (e.g. care package or care home residency).
- Immobility and Falls Risk: Timed Up and Go Test at baseline (day 1) and 72 hours on completion of the intervention period (22); a trained member of staff should record the time (in seconds) that it took the participant to rise from a chair, walk approximately three metres, turn around, walk back to the chair and sit down This will *only* be undertaken if the participant is deemed safe to mobilise by the clinical team, is comfortable to undertake this test and a trained member of staff is available. Immobile patients will be scored 0.

Qualitative interviews: Purposely selected patients, people with carer responsibilities (e.g. Personal Consultees, or equivalents in Scotland, or other subsequent carers) and healthcare professionals will be interviewed for qualitative analysis by the trial qualitative researchers (timing of interviews is flexible; see section 13 for further details, below).

12.3 72-hour data collection (intervention period)

Questionnaire (participants with aid of researcher/clinical team where necessary): Participants will be asked to complete the 72-hour study questionnaire booklet over the course of the 72 hours (or up until point of discharge if sooner) which contains (at least) the following PROM:

- Total pain experienced over the 72 hours period, derived by the standardised area under the curve (scaled from 0 to 100) of each participants' 4 hourly pain score using a self-reported VAS. The VAS is presented as a 100 mm horizontal line with verbal anchors at each end of 'no pain' and 'worst pain possible'. The study participant selects the point along the line (and marks this point with a pen) that reflects their current pain perception. Participants record VAS scores at 4 hourly intervals over a 12-hour period. Periods of sleep are also recorded retrospectively by the participant. For patients who have mild/moderate cognitive impairment the VAS may be completed with the assistance of a researcher/member of the clinical team; if in such participants it becomes unfeasible to complete the questionnaire (or elements of it), site staff should record this in the 72-hour CRF.

CRF (site staff): A research nurse, or other delegated site staff member, will complete the 72-hour CRF over the course of the 72 hours (or up until point of discharge if sooner). CRF contents are derived from outcome measures to include (as a minimum):

- The Abbey pain scale (designed for use in non-verbal patients with dementia (26)) will be recorded in all patients daily for the 72-hour intervention period by a trained member of staff/researcher, to determine the feasibility of using this scale across the whole study population. The pain scale is a movement-based assessment, therefore the researcher observes the participant while they are being moved and records the results within the CRF.
- Total opioid consumption in the first 72 hours of attendance: Total opioid dose is recorded from the prescribed medication administered as recorded on the patient's ambulance care record, ED drug chart or inpatient drug chart during the first 72 hours of attendance
- Record of treatments received; if cross-over occurs then details, including reason(s) why, should be recorded
- Screening for the development of relevant frailty syndromes will be undertaken from notes screening by a trained researcher/member of site staff:
    - Delirium: daily assessment of 4-AT brief clinical instrument for delirium detection (23) for 72 intervention period collected by a researcher
    - Immobility and Falls Risk: Timed Up and Go Test at baseline (day 1) and 72 hours on completion of the intervention period (22)
- Opiate induced constipation: stool frequency and Bristol Stool Form Scale (24) recorded from patient notes at 72 hours on completion of intervention period collected by a researcher (41)
- Adverse events.

NB: For patients discharged prior to 72 hours, data collection for this particular time point will cease following discharge.

12.4 30-days (+10-days)* post injury (randomisation) data collection and follow-up

Hospital (site) research teams (or delegated equivalent) are responsible for conducting the 30-day (final) follow up, with the support of the central trial team (study office), if required and where feasible.

Questionnaire (participants):

Participants who remain in hospital at 30-days post-randomisation (+10 days): a member of the research team will ask these participants to complete the 30-day study questionnaire (paper booklet or online equivalent if preferred and feasible). This will contain (at least) the following PROMS:

- EQ-5D-5L (27)
- ICECAP-O (28-30)
- Chest Trauma Score (RibPROM).

For patients who have mild/moderate cognitive impairment, the questionnaire may be completed with the assistance of a researcher/member of the clinical team (or person with caring responsibility if/where feasible); if in such participants it becomes unfeasible to complete the questionnaire (or elements of it), site staff should record this in the 30-day CRF.

Participants who have already been discharged from hospital: a member of the research team will contact these participants (and/or person with caring responsibility, where applicable) around 30 days (+10 days) after their initial attendance (post-randomisation) to complete the 30-day study questionnaire. Prior to contact, the researcher will check that the patient is still alive to mitigate any risk (plus capacity status, where feasible**). Where appropriate, a researcher will send a copy of the questionnaire by post, including an approved cover letter and pre-paid envelope for return directly to the central trial team (study office); the central trial team (study office) will notify sites when questionnaires are returned. Alternatively, the questionnaire can be completed online or over the telephone (or alternative method if requested and where it is appropriate and feasible, e.g. Sponsor/NHS-approved video/tele-conference platforms) with a trained researcher if preferred. In line with the Mental Capacity Act 2005, where data are collected via remote questionnaires (i.e. not in-person), consent (and capacity) is typically implied by return of the questionnaire, so the researcher need not proactively monitor capacity.

If a participant response is not received within a reasonable time (e.g. ~2-3 weeks), then a researcher will try contacting the participant (and/or carer) to complete the questionnaire, and/or resend another pack if appropriate/requested. The researcher will make (up to) three contact attempts on different occasions (allowing at least 7 days between contacts). The feasibility of these follow-up processes will inform the definitive trial.

**While researchers are expected to complete hospital screening, CRFs, and send initial questionnaires within the desired timeframe (30+10-days), we anticipate the need for flexibility regarding participant responses, especially if they have been discharged from hospital. Therefore, we foresee that participant responses may be outside this period. Understanding participant response rates is a key feasibility outcome.*

***Capacity status in participants who have already been discharged will be checked via medical notes, where feasible. It is also possible that a person with caring responsibility may inform the research team of any changes. If at 30 days it becomes apparent that a participant who did not originally have capacity has potentially regained capacity, the patient will be contacted directly by a member of the hospital (site) research team. The researcher will formally assess capacity and capture retrospective consent if appropriate, which can be done remotely in such cases.*

<u>*CRF (site staff):*</u> A research nurse, or other delegated site staff member, will complete the 30-day CRF. CRF contents are derived from outcome measures and will be collected up until 30 days following randomisation from medical notes and GP records (where available electronically). Content includes (as a minimum):

- Pulmonary complications
- Development of acute delirium during inpatient stay
- Change in participant's capacity status (if applicable)

- Hospital discharge details, including discharge destination and support requirements (where relevant)
- Hospital re-admission
- Mortality
- Adverse events
- Total length of hospital stay (calculated from electronic patient tracking systems to include length of stay in the ED and inpatient length of stay). If >30 days, actual discharge date will be collected where feasible as this will inform the follow-up period for the definitive trial. Cut-off for this, however, is where participants remain in hospital at the point of follow-up completion for the final participant; length of stay will be recorded as >30 days if appropriate
- Hospital resource use data, to include need for Intensive Care Unit Admission.

12.5 Outcome adjudication

Where possible, outcomes (principally the presence of adverse pulmonary outcomes) *may* be verified by one local ED investigator (site PI) and adjudicated by an independent assessor (Respiratory Physician) with reference to relevant clinical information uploaded anonymously to the study database/relevant depository. Disagreement will be resolved by discussion. We will assess the feasibility of this to inform the main trial.

13 INTEGRATED QUALITATIVE STUDY

13.1 Interviews with patients and people with carer responsibilities

To explore details of the study design, acceptability of proposed outcome measures to patients and understand recruitment processes for the main trial, up to 24 participants who agreed to further contact during initial consent (in a ratio of 2:1 intervention:control, from at least 3 sites) will be invited to take part in a semi-structured interview with a qualitative researcher or the CI (following appropriate training). We will also invite six Personal Consultees with carer responsibilities (or equivalent legal representatives in Scotland) and/or other subsequent carers (e.g. relative, home care or nursing home staff) to take part. These interviews will be conducted via telephone (or alternative method if requested and where it is appropriate and feasible, e.g. Sponsor/NHS-approved video/tele-conference platforms, or face-to-face) around one month (and up to 90 days) after randomisation. Verbal informed consent to participate in qualitative interviews will be recorded (at the beginning of audio recording and on the Interview Verbal Consent Record Form completed by the interviewer). A purposive sample will be selected to reflect maximum variation in socio-demographics, age, and ethnicity. The interviews with people with carer responsibilities (e.g. Personal Consultees, or equivalents in Scotland, or other subsequent carers) will also explore consent processes in patients with cognitive impairments.

All potential interviewees will be provided with an appropriate Interview PIS; a hard copy may be posted/emailed, and an electronic version will be available via the study website for review and download. Topic guides for the interviews will be developed from the literature, team discussions and input from the PAG.

13.2 Patients who decline to be randomised into the trial

If a potentially eligible patient decides that they do not want to take part in the trial following an invitation, a member of the research team will ask them about why they declined to participate. This is so that the study team can identify and understand if recruitment processes need to be improved. Patients will only be asked for their reasoning at one single time point, which will be soon after they decline. It is acknowledged, however, that patients are not expected to provide a reason if they do not want to. The researcher will record relevant information on the study screening log (identified in section 8.5).

13.3 Focus groups with healthcare professionals (HCPs)

After completing focus group training, the CI will lead two focus groups (including up to ten HCPs per focus group) with at least two sites. Specialists from emergency medicine/care of the elderly/pain medicine, a research nurse and clinical nurse specialists will be provided with a HCP Focus Group PIS and invited to take part, to evaluate their experiences of treatment and views of trial processes, including evaluating equipoise around the use of the intervention. Where necessary, the focus groups will take place remotely, using Sponsor/NHS-approved video/tele-conference platforms.

To capture the informed consent of all focus group participants accurately, HCPs who are willing to take part will be asked to provide written informed consent. To enable remote and/or face-to-face methods of contact, HCP informed consent will be captured via an eConsent (online) form (via a REDCap database system and process). Three copies (paper print out and/or electronic) of the completed consent form are required: (1) a copy must be filed in the ISF together with a copy of the relevant information leaflet in recruitment order; (2) a copy should be given to the participating member of staff; and (3) a copy should be retained by the RELIEF central trial team (study office).

When an eConsent Form is completed and processed, a copy is emailed to the participant automatically *if* they provided an email address. Additional copies can be obtained via the eConsent (database) system and will be provided/filed as required, by the qualitative researcher (or delegate).

If eConsent is not feasible, an approved paper (wet ink) equivalent will be available. As above, three copies of the completed consent form are required; when a paper (wet ink) form is completed, the ‘original’ should be filed in the ISF.

13.4 Analysis

With informed consent, all interviews and focus groups will be audio recorded (using an encrypted audio digital recorder), transcribed, anonymised, and analysed using thematic methods of building codes into themes and sub-themes (facilitated by NVIVO software (42). Analysis will be ongoing and iterative. The CI and a qualitative researcher will code a sample of transcripts independently, compare coding, discuss, and resolve any discrepancies within the research team to achieve a coding consensus and ensure robust analysis. Further details about the management of the qualitative research data can be found in section 19, Data Management.

14 NESTED HEALTH ECONOMIC SCOPING

An evaluation of the feasibility of identifying and measuring health economics outcomes data will be completed as part of the trial. As this is a feasibility trial, the focus will be on establishing the most appropriate outcome measures for inclusion in a future economic evaluation alongside the definitive trial. The EQ-5D-5L patient reported questionnaire (27) will be completed at baseline, to capture retrospective pre-injury state and baseline post injury state*, and 30 days post randomisation. The ICECAP-O (28-30) and The Chest Trauma Score (RibPROM), a 32-item PROM assessing quality of life after rib fracture (noted in section 4.4), will also be collected at 30-days. In addition, information on key resource use as outlined in the 30-day CRF and to include length of stay, intensive care use and medication prescribing will be collected. This element of the trial will be led by the CI, with guidance from a Health Economist at the UoB.

**At baseline, a modified version of the EQ-5D-5L patient reported questionnaire will be completed twice to capture (i) retrospective pre-injury state and (ii) baseline post injury state. The EQ-5D-5L patient reported questionnaire asks people to reflect on their health "TODAY"; for the purpose of this feasibility trial, at baseline (only) we expect to replace "TODAY" with "BEFORE INJURY HEALTH" and "AFTER INJURY HEALTH (TODAY)", with support of the EuroQol Research Foundation.*

15 SAFETY

Serious and other adverse events (S/AEs) will be recorded and reported in accordance with the GCP guidelines and the Sponsor's Research Related Adverse Event Reporting Policy. Participant safety will be monitored by the Trial Management Group (TMG), Sponsor and Trial Steering Committee (TSC) and the trial will be stopped if any indication of harm from using the intervention is found.

15.1 Definitions

Adverse events

Term	Abbreviation	Definition
Adverse Event	**AE**	Any unfavourable and unintended sign or symptom that develops or worsens during trial participation, whether or not it is considered to be related to the trial intervention. In all instances, it will be up to the PI of each participating site (or appropriate delegate, e.g. clinician) to determine whether the person's change in health is related to the trial. AEs are not continuous and persistent disease or symptoms, present before the trial, which fail to progress; signs or symptoms of the disease being studied (in this case pulmonary complications or development of frailty syndromes); or treatment failure.
Adverse Reaction	**AR**	The distinguishing feature between an AR and AE is whether there is evidence to suggest there is a causal relationship between the event and the research procedure.
Serious Adverse Event	**SAE**	Any untoward medical occurrence that: • Results in death • Is life threatening[A] • Requires hospitalisation or prolongation of existing hospitalisation[B] • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Or is considered by the investigator to be an important medical event [A] *The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.* [B] *The definition of hospitalisation is an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Accident & Emergency Department (A&E) would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.*

Serious Adverse Reaction	**SAR**	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure.
Suspected Unexpected Serious Adverse Reaction	**SUSAR**	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is unexpected
Accidents Incidents or near Misses	**AIMS**	The AIMS system is common in many NHS Trusts and implements and NHS Trust's policy on Incident Reporting – including relevant AEs that occur in relation to research and during normal clinical practice.

Severity classifications

Mild event	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event	An event that prevents normal everyday activities.

Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

15.2 Identification of adverse events

Adverse events (AEs) are likely to occur throughout the course of the trial. AEs may be volunteered by the participant or detected by a member of the research team through questioning or observation, during either the index hospital attendance or the follow-up contact. Local research teams are responsible for assessing *all* AEs that they become aware of for their participants during the trial, i.e. those occurring from when a patient signs the written consent form until the 30-day follow-up time point. Recording and reporting details of AEs are outlined, below (sections 15.4 and 15.5).

15.3 Classification of all adverse events

The PI of each participating site (or appropriate delegate, e.g. clinician) is responsible for assessing all AEs and categorising whether they are serious, expected, and related. A list of events that can be expected during this trial, or within this patient population can be found below; other factors such as participant history should not be taken into account.

The following events can be expected during this trial, or within this patient population:

- Pulmonary complications such as pneumonia, which may cause death
- Frailty syndromes such as delirium and constipation
- Prolonged hospitalisation due to complications from initial injury
- Prolonged hospitalisation due to social care needs
- Pressure sores due to immobility
- Minor skin irritations (including tears) due to lidocaine patch application. In the clinical experience of our geriatricians and acute pain team experts this is very unlikely to occur.

15.4 Recording and reporting non-serious adverse events (AEs)

A non-serious AE is an adverse event which does not satisfy the definition of a serious adverse event (SAE); see section 15.1 above, Definitions – Adverse Events.

Following assessment, only non-serious AEs considered to be **possibly, probably, or definitely related to the use of the intervention (i.e. lidocaine patches) and/or study procedures** will be recorded in the relevant study documentation (e.g. CRF). They should also be recorded in the participants' clinical notes, by the research nurse or other suitable member of the research team. The participant should be followed up by the hospital (site) research team until the event subsides. The recording framework for non-serious AEs is shown in ***Figure 4***, below. A record of all recordable AEs must be kept in the ISF.

If the event is defined as 'serious' (SAE), the hospital research team should proceed to follow recording and reporting procedures for SAEs, outlined below (section 15.5).

<u>CRF data capture will include (as a minimum):</u>

- a description of the event
- the date/time that it started and stopped
- the severity of the event
- details of any actions taken in response to the event.

The central trial team (study office) will prepare regular summary reports of all recorded non-serious AEs for discussion at relevant trial oversight meetings, including with the Sponsor.

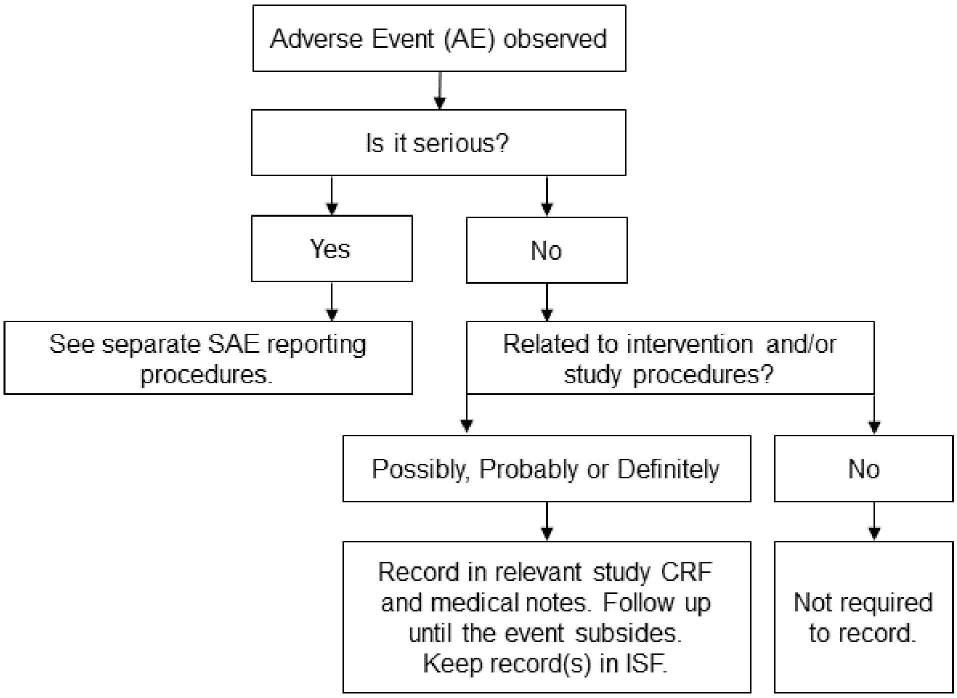


Figure 4 Recording framework for AEs assessed as non-serious.

15.5 Recording and reporting serious adverse events (SAEs)

Local research teams will record **all SAEs** in the study SAE Summary Log, which will be filed in the ISF. A copy of this will be securely transferred to the central trial team (study office) on a regular basis (e.g. monthly) for monitoring and reporting purposes. The central trial team will prepare regular summary reports of SAEs for discussion at relevant trial oversight meetings, including with the Sponsor.

Furthermore, all SAEs will be recorded on relevant study documentation (e.g. CRF). They should also be recorded in the participants' clinical notes, by the research nurse or other suitable member of the research team. The participant should be followed up by the hospital (site) research team until the event subsides. The PI, or delegate, should complete the overall assessment. Information not available at the time (such as test results) must be forwarded once available.

- **Expected SAEs** will be recorded (as noted above) and reported to the Sponsor routinely by the central trial team, but do not require expedited reporting to the Sponsor *unless* they are fatal. **Expected SAEs which ARE fatal** will be reported to the Sponsor within 24 hours of staff becoming aware of the event, as detailed below.

- **Unexpected SAEs** will be reported to the Sponsor within 24 hours of staff becoming aware of the event. **Any unexpected SAEs which ARE causally related to the intervention/ research procedures** will also be reported to the REC immediately (must be within 7 days if fatal, or 15 days if non-fatal) by the central trial team. Local reporting of clinical events related to patches should also be reported through local adverse event reporting systems such as DATIX and managed according to local governance processes.

NB: *Lidocaine patches have been used since 1999 for the treatment of shingles. Numerous studies have evaluated safety of the patches and no clinically significant systemic adverse effects have been noted, including when used in an elderly population in high doses (12). Therefore, we do not anticipate any unexpected SAEs in relation to the intervention.*

All SAEs that require expedited reporting to the Sponsor (i.e. expected SAEs which are fatal, and all unexpected SAEs) must be documented on the full SAE/SAR Initial Report Form, which is provided by the central trial team. (An initial report may be provided orally but a written SAE/SAR Initial Report Form must be completed within 24 hours of staff becoming aware of the event). Reporting process:

- **Sites** should scan and email the form, with high importance, to the (i) Sponsor, (ii) RELIEF central trial team (Trial Manager), and (iii) cc'd Dr Edward Carlton, Chief Investigator; see **'Key Trial Contacts'** for contact details (pages 2-3).

*(**Please note**: typical University (central trial team) staff working hours are Monday to Friday, 09:00-17:00 (subject to variation). In the event of University closure dates or limited availability, an out of office automatic response will notify the site of alternative contact details/arrangements).*

- The **Sponsor and/or central trial team** will confirm receipt and, if required, forward the completed form to REC within the reporting periods (see below).

For each SAE reported to the Sponsor, the following information (as a minimum) will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to research procedures), in the opinion of the PI
- Whether the event would be considered expected or unexpected.

Each SAE must be reported to the Sponsor separately and not combined on one SAE form.

Any change of condition or other follow-up information relating to a previously reported SAE should be documented on the separate SAE/SAR Follow Up Report Form provided by the central trial team.

As above, sites should scan and email the form to the relevant personnel who will confirm receipt, and if required, forward it to the REC within the necessary timeframes.

Events will be followed up until the event has resolved or a final outcome has been reached.

Figure *5* below summarises the SAE safety reporting requirements.

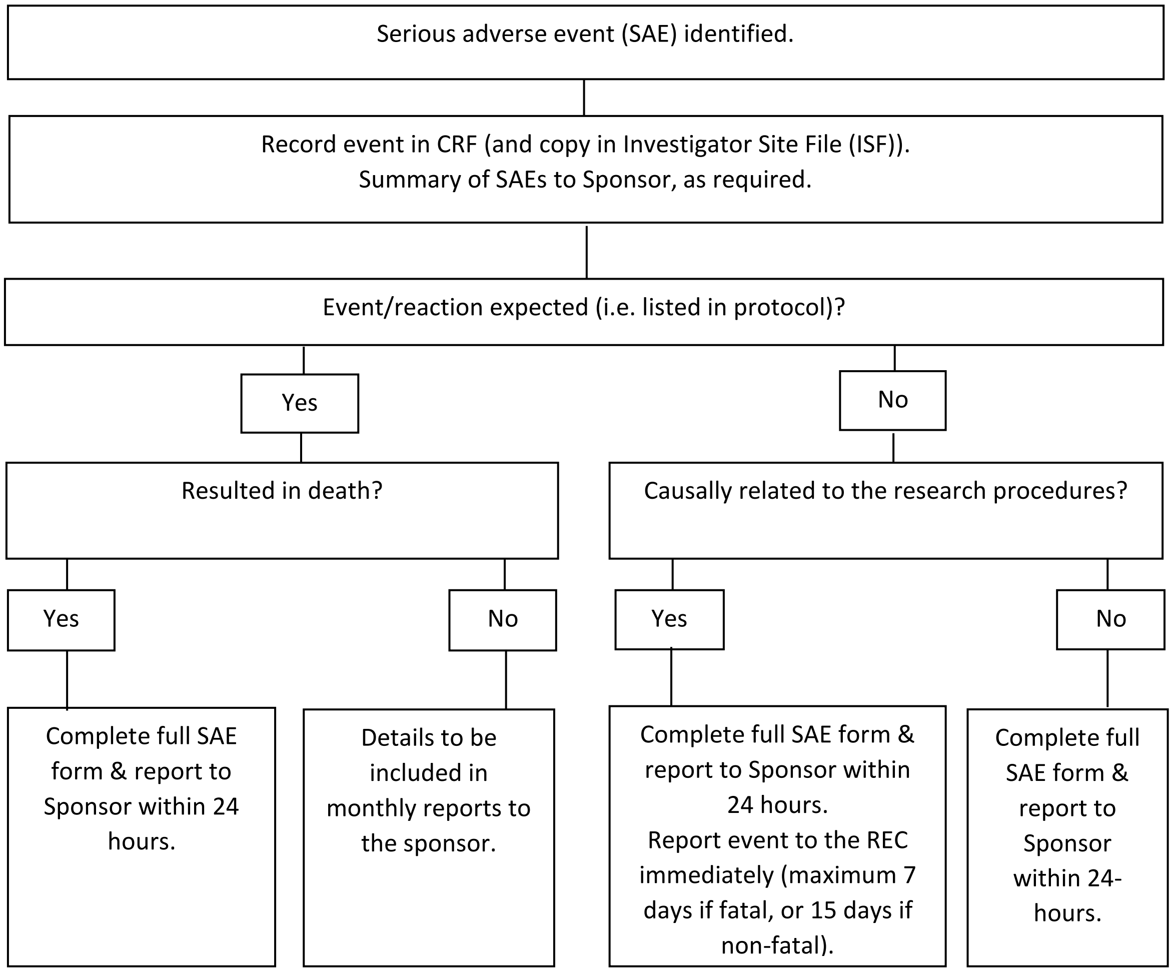


Figure 5 Overview of safety reporting requirements for AEs assessed as being serious (SAEs)

15.6 Responsibilities

All adverse events will be documented and reported in accordance with North Bristol NHS Trust's Safety Reporting Standard Operating Procedure (SOP) and as above, agreed by the Sponsor.

Principal Investigator (PI)/research nurse. PIs and research nurses (or suitably trained delegates) at each site will be checking for AEs when participants attend for treatment/follow-up, and at specified data collection points. The appropriate persons will be responsible for:

- Using medical judgement in assessing and assigning seriousness, causality and expectedness.
- Ensuring that all appropriate AEs are documented.
- Ensuring that all SAEs are recorded and reported as per the procedures noted above, including the provision of further follow-up information as soon as available.
- Ensuring that SAEs are chased with the Sponsor/central trial team if a record of receipt is not received within 2-working days of initial reporting.
- Investigators should also comply with any internal SAE reporting requirements within their host institution.

Chief Investigator (CI). The CI (or agreed delegate) will be responsible for:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assessing and assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of SAEs requiring expedited reporting.
- Ensuring safety reports are prepared in collaboration with appropriate members of the TMG group for the relevant oversight committees and regulatory authorities.
- Expedited reporting of SAEs to the REC within required timelines.
- Notifying PIs of SAEs that occur within the trial (where applicable).
- Central data collection of SAEs.

Trial Manager. The Trial Manager will provide a summary of S/AEs to the TSC and Sponsor as required.

16 STUDY COMPLETION

Individual participants will normally complete the study after the 30-day (+10 days) follow-up has been completed. The study itself will end when the last participant has completed the 30-day follow-up, all qualitative interviews have been completed (up to 90 days after initial ED attendance), and all data has been finalised (all data queries have been resolved and the study database has been locked).

16.1 Premature termination of the study

If the TSC or Sponsor recommends early termination of the study for any reason, the CI will notify the Funder and relevant regulatory authorities (e.g. REC). If the trial is prematurely terminated, no new participants will be recruited, and a decision on data collection on active participants will be made in discussion with the TSC and Sponsor. The CI will be responsible for informing participating sites of the premature termination of the study.

17 PARTICIPANT WITHDRAWAL

Participants can choose to withdraw for any reason at any time during their involvement in the trial without affecting their usual care; they do not have to provide a reason for doing so. Participants can withdraw from (a) complying with the allocated trial treatment or (b) the trial completely. If a participant wishes to withdraw from receiving the allocated trial treatment, efforts will be made to continue to obtain future questionnaire/assessment data with the permission of the patient or relevant (legal) representative, as appropriate. In both cases efforts will be made to report the reason for withdrawal as thoroughly as possible in a study specific Change of Permissions/Withdrawal Form.

In the event the clinician feels it is unsafe for the participant to continue in the study, s/he can withdraw the participant from the study. Furthermore, if the Personal or Nominated Consultee (or legal representative in Scotland) of a participant advises the research team that the participant should be withdrawn from the study, the research team must withdraw them.

In all cases, the study would retain, confidentially, any data collected up to the point of withdrawal for analysis. Furthermore, as advised in the study information documents, we would continue to collect data from their electronic medical records unless they request otherwise.

Participants who withdraw (or are withdrawn) from the study at any stage following randomisation will not be replaced within the study.

17.1 Participants who lose capacity during the 30-day trial period

If a participant loses capacity during their trial involvement and they are withdrawn from the trial, any data already collected up to the point of withdrawal will be retained, as noted in the study information material and consent form.

17.2 If a patient (participant) regains capacity during the 30-day trial period

If a patient, who lacked capacity at point of trial enrolment, regains capacity during their trial involvement and does *not* wish to continue participation (i.e. does not provide retrospective consent), they will be withdrawn from the trial. Permission will be sought to retain and analyse any data already collected (up to the point of withdrawal); if, however, the patient does not give permission to retain and analyse the data, it will be destroyed. Where appropriate, permission will also be sought to continue collecting follow up data from central medical records.

Trial specific instructions will be provided to participating sites for withdrawal criteria and procedures.

18 STATISTICAL CONSIDERATIONS

18.1 Sample size

As this is a feasibility trial a formal sample size calculation based on statistical power to detect a specified treatment effect size is not appropriate. In line with published "rules-of-thumb" and on a pragmatic basis we have determined that a total sample size of 100 (50 per arm) will be sufficient to provide estimates of recruitment, retention, data completion and adherence (43). Recruitment will take place over an 18-month period.

18.2 Statistical analysis and progression criteria

The analysis will focus on reporting feasibility measures (eligibility, recruitment, retention and data completeness). Data will be analysed and reported following the CONSORT guidance extension to feasibility studies (37) and will include a CONSORT flow diagram, descriptive and summary statistics both overall and by treatment arm. Feasibility parameters required to progress to a full trial are presented in ***Table 4***, below.

This study is not powered to carry out hypothesis testing. Descriptive statistics for the patient characteristics and clinical outcome data will also be reported overall and by treatment group; as means or medians with measures of dispersion for continuous outcomes (as appropriate given the form of their distribution) and frequencies and percentages for categorical outcomes.

Table 4 Feasibility parameters required to progress to a full trial

	Participants	Anticipated action
Go (Green)	• **Recruitment:** >70% of expected recruitment. • **Follow Up:** ≥75% of data for suggested primary outcome of 30-day pulmonary complications. • **Adherence:** ≥75% adherence to the intervention.	Continue to main trial.
Amend (Amber)	• **Recruitment:** 50-70% of expected recruitment target. • **Follow Up:** 65-74% of data for suggested primary outcome of 30-day pulmonary complications. • **Adherence:** 65-74% adherence to the intervention.	Identify remediable factors, discuss with TMG and TSC.
Stop (Red)	• **Recruitment:** <50% of expected recruitment target. • **Follow Up:** <65% of data for suggested primary outcome of 30-day pulmonary complications. • **Adherence:** <65% adherence to the intervention.	Do not progress to main trial, unless there is a strong case that unanticipated remediable factors have been identified and can be addressed after further discussion with the funder.

19 DATA MANAGEMENT

19.1 Source data and documentation

Source data is the first place the data is recorded. Source data for this trial will consist of paper or electronic (where eConsent has been taken) copies of the consent form(s) (plus verbal consent for qualitive interviews with patients and people with carer responsibilities), participant completed questionnaires (paper and/or electronic), paper CRFs designed specifically for the study, and audio-recordings of interviews. Where data is recorded first in the patient's medical records that is, and will remain, the primary source data. Any specifically designed CRFs would be considered supplementary source data.

Each participant will be allocated a unique study I.D number at the point of providing informed consent (advice). Participants will be identified in all study-related documentation by (at least) their study I.D number. A record of trial participants' names and contact details (and, where relevant, their Consultee or equivalent representative in Scotland), hospital numbers and assigned trial numbers will be retained by the research nurse at each site and stored securely for administrative purposes (in the ISF, for example). Personal data entered directly into the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to relevant members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the European Economic Area (EEA) will be anonymised.

Participants will be informed via the information documents and consent form that personal information such as their name, email address and phone number will be stored on the secure database with the central trial team (study office, University of Bristol). Furthermore, for the purpose of conducting the trial randomisation only, participant information (including personal details, such as unique study I.D. number, study site, gender, and date of birth) will be entered into the secure online randomisation system provided by Sealed Envelope™ (38). All data that are entered on to the Sealed Envelope™ system is done so via secure sockets layer (SSL) connections and stored on secure servers located in the UK and Ireland that comply with both UK and EU regulations on data privacy. User-access to the system will be managed by the central trial team (study office), who will in turn generate password-protected user-accounts for authorised centre/site staff.

Data obtained by paper will also be entered onto the password protected database (by trained members of site and/or central trial staff). Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to RELIEF trial staff. Information capable of identifying participants will not be removed from clinical sites apart from when securely transferring data to the central trial team at the University of Bristol. This data will not be made available in any form to those outside the trial, with the exception of inspection purposes by the sponsor and/or other regulatory authorities. Consent forms and clinical letters (and any other documentation) with personal identifiable data will be stored in a locked filing cabinet (or locked equivalent). Participant details will be anonymised in any publications that result from the trial.

Qualitative interview data. Interview data captured on an encrypted audio digital recorder will be uploaded to a University of Bristol computer as soon as possible after each interview. All audio-recorded data will be stored on a password protected computer maintained by the University of Bristol. Audio-recordings will be transcribed by University of Bristol employees or University-approved transcription services. Audio-recordings and transcripts will be labelled with a unique study I.D number, edited to ensure anonymity of respondents, and stored securely adhering to the University's data storage policies.

Anonymised quotations and parts of voice-modified recordings may be used for training, teaching, research and publication purposes for this and future studies. Anonymised transcripts may be made available to other researchers who demonstrate compliance with legal, data protection and ethical guidelines for purposes not related to this study, subject to individual informed consent from participants (this includes trial participants (patients), people with carer responsibilities, and HCPs). At the end of the study, anonymised data (including transcripts of audio-recordings) will be stored in a secure research data storage facility, alongside the other study data; see sections 19.4-19.7 below, for further details.

19.2 Data collection

Data collection is detailed in section 12, above (and throughout).

Data will be recorded directly into CRFs and questionnaires (paper and/or online), and where applicable, will either be entered at site by delegated clinical/research site staff into a trial specific database, or transferred securely (electronically or by post) to the central trial team (study office, University of Bristol) for entry into the trial specific database.

The eConsent (online) forms and online questionnaires will be completed via the REDCap database system and process (see below for REDCap details), which can be securely accessed via the internet. It is expected that participating sites will be provided with a study-specific tablet device (with a wipeable screen and cover), which would be handed to the participant to support this process, where feasible. In such cases, the tablet device would be password protected and only used by the research team or authorised clinical team for study-purposes.

19.3 Database platforms

All administrative and clinical study data will be stored in a REDCap database. REDCap is a secure, web-based electronic data capture (EDC) system designed for the collection of research data. The system has been developed and supported by Vanderbilt University. The Bristol Trials Centre (BTC) at the University of Bristol (UoB) has set up its own infrastructure so that all systems are hosted at and supported by UoB.

A Relational Database Management System will be used to provide integration services between administrative and clinical databases. These data will be stored here, to support the workflow of the study team. These data will be not made available for analysis. These data are stored in a SQL Server system maintained by UoB.

19.3.1 Administrative Data

Administrative data will be kept in a secure REDCap database that is only accessible from within the UoB firewall. All users will require (at least honorary) contracts with UoB to access it.

19.3.2 Clinical Data

The clinical data will be stored on a separate server to the administrative data. Anonymised clinical data is linked by a study participant I.D. If an email address is collected, the 'Email Address' field is flagged as an identifier and not included in the export for the statistician, so the data set can be considered pseudonymised at export and does not need further processing.

19.4 Data storage

North Bristol NHS Trust and the Bristol Randomised Trials Collaboration (University of Bristol) are joint data controllers for the RELIEF Trial. Data will be held at the University of Bristol and will conform to the University of Bristol Data Security Policy and in Compliance with the General Data Protection Regulation (GDPR) as it applies in the UK, tailored by the Data Protection Act 2018.

19.5 Access to Data

For monitoring purposes, the CI will allow monitors from the Sponsor (or delegate), persons responsible for the audit, representatives of the REC and other Regulatory Authorities to have direct access to source data/documents.

The Trial, and Data, Manager (in collaboration with the CI) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

19.6 Archiving and destruction of trial materials

An archiving plan will be developed for all trial materials. Data will be held in compliance with the Sponsor's SOPs. All research data will be retained in a secure location during the conduct of the trial and for at least 5 years after the end of the trial. Medical case notes containing source data or other trial-related information should be identified by a label (or equivalent for electronic notes, where feasible) "Keep until at least dd/mm/yyyy" where the date given is at least five years (or applicable period) after the end of the trial. Data will be kept at the University of Bristol (and/or Sites) for this time and, at the end of the archiving period, will be destroyed by confidential means with the exception of a final trial dataset which will be made available for data-sharing purposes (see section 19.7 below). Where electronic records are in use, University of Bristol and/or North Bristol NHS Trust's policy will be followed. The approval of NBT as owner of data and Study Sponsor, as well as the CI, will be sought prior to destruction of the data.

Participating sites will be responsible for ensuring that all study records held at site are archived appropriately when notified by the Sponsor / BTC (central trial team).

19.7 Access to the final trial dataset

Anonymous research data, which may include qualitative audio-recordings and/or associated data such as anonymised transcripts, will be stored securely and kept for future analysis with participant consent. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on research data storage facility (RDSF). Requests for access to data must be via a written confidentiality and data sharing agreement (DSA) available from the RDSF website which will be confirmed by the CI (or appointed nominee).

The DSA should cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

20 TRIAL MANAGEMENT

The CI will take overall responsibility for managing the various components of the trial, with the support of the BTC trial manager, and will meet with other relevant personnel (as required) for each component. The BTC, a UK Clinical Research Collaboration (UKCRC) registered trials unit, will support the delivery and conduct of the trial.

20.1 Trial Management Group (TMG)

The project will be led by the trial management group (TMG) which will include the CI, the BTC trial manager, trial statistician and other relevant personnel (e.g. clinical colleagues, BTC representatives, Sponsor representative, as required). The TMG will meet regularly throughout the duration of the trial to ensure development of study documentation and approvals, monitor progress (including participant recruitment), resolve day-to-day problems as they arise, review the budget, discuss analysis, results, draft reports and dissemination.

20.2 Trial Steering Committee (TSC)

The TSC will oversee the conduct and safety of the trial, ensuring that milestones are achieved and general scientific probity is maintained. The TSC will monitor progress of the trial, adherence to the protocol and consider new information of relevance to the research question. In the absence of an independent Data Monitoring Committee, the TSC will also oversee the safety and ethics of the trial, reviewing recruitment, primary outcome data completeness and adverse events data. The TSC will include an independent chair (ED clinician), independent care of the elderly physician, an independent lay representative, an independent statistician, and a (non-independent) senior member of the research team and the CI.

20.3 Patient and Public Involvement (PPI)

The PAG will be actively involved in the design and development of trial-specific patient information resources, follow-up questionnaires, topic guides for interviews and methods for enhancing recruitment and follow-up rates.

Our PAG has four members who are expected to meet on at least four occasions to advise the management team. They will be offered a study specific induction pack which will include the INVOLVE Public Information Pack (or suitable equivalent) and relevant study information. Training workshops will also be provided by People and Research West of England. PAG members will have their travel expenses and meeting time reimbursed either with vouchers or a meeting payment based on INVOLVE (or suitable equivalent) guidance.

We will consult with the PAG when we analyse and interpret the data from this study. Findings will be presented in lay terms at a PAG meeting. We will then seek the group's interpretation of the findings as a guide to whether a definitive trial will be feasible. They will advise us on routes for dissemination to patient groups and the best format for this.

20.4 Sponsor

The study Sponsor is North Bristol NHS Trust. Selected sponsorship responsibilities will be formally delegated to the BTC under the terms of an appropriate service level agreement.

20.5 Funding

The trial is funded by an Advanced Fellowship from the National Institute for Health Research (NIHR300068). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

21 MONITORING, AUDIT AND INSPECTION

The study will be monitored in accordance with the Sponsor's (North Bristol NHS Trust) Monitoring SOP, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by North Bristol NHS Trust, the Research Ethics Committee (REC) and available for inspection by other licensed bodies.

A trial monitoring plan will be developed by the Sponsor and agreed by the TMG and CI based on the trial risk assessment which may include on site monitoring.

The Sponsor usually delegates some of the monitoring to the central trial team. The following checks would be typical:

- That consent is taken by an appropriately authorised person
- That informed consent has been properly documented
- That data collected are consistent with adherence to the trial protocol
- That CRFs are only being completed by authorised persons
- That SAE recording, recording of protocol deviations and reporting procedures are being followed correctly
- That no key data are missing
- That data is valid
- Review of recruitment rates, withdrawals, and losses to follow-up.

21.1 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms and reported to the CI and sponsor. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, TMG and the TSC.

A serious protocol breach will be reported to the Sponsor as soon as possible. The sponsor will determine the seriousness of the breach and whether onward reporting to the REC is necessary.

21.2 Notification of serious breaches to GCP and/or the protocol and poor-quality data

A "serious breach" is a breach which is likely to affect to a significant degree:

a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial.

The Sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per appropriate Sponsor SOP. Repeated major breaches may be considered serious breaches and notified to the REC and Health Research Authority (HRA).

22 ETHICS AND REGULATORY APPROVALS

22.1 Research Governance

The study will be undertaken at several UK sites, subject to appropriate REC approval and HRA approval. The trial will be conducted in accordance with the protocol, the conditions and principles of the Declaration of Helsinki and GCP. Any amendments of the protocol will be submitted to the REC for approval. On request, the study investigators and their institutions will permit trial-related monitoring and audits by the Sponsor and relevant REC by providing direct access to source data and other documents (i.e. patients' hospital notes, X-ray reports etc. where relevant).

22.2 Governance and legislation

This trial will be conducted in accordance with:

- Conditions and principles of GCP guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act (DPA) 2018
- General Data Protection Regulation (GDPR)
- Mental Capacity Act 2005
- Adults with Incapacity (Scotland) Act 2000

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the REC.

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a greenlight letter.

For all amendments the CI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

This research trial will be conducted in accordance with conditions and principles of GCP. GCP is the international ethical, scientific, and practical standard to which all clinical research is conducted. Compliance with GCP provides public assurance that the rights, safety, and well-being of people taking part (trial participants) are protected and that research data are reliable.

22.3 Research Ethics Committee (REC) review and reports

Ethics review of the trial protocol and other trial related participant facing documents will be carried out by a UK REC. HRA approval will be sought alongside REC. Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF)/ISF.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI (or designee) will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI (or designee) will submit a final report with the results, including any publications/abstracts, to the REC.

GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

22.4 Peer Review

The proposal for this trial has been peer-reviewed through the NIHR peer-review process, which includes independent expert and lay reviewers.

22.5 Poor quality data

The quality of the trial data will be monitored throughout the trial and data completeness will be reported to the TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

22.6 Financial and other competing interests

This applies to the chief investigator, PIs at each site and committee members for the overall trial management. Research team, trial committee members and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

22.7 Risks and benefits

We believe this study does not pose any specific risks to individual participants, nor does it raise any serious ethical issues.

As with all trials the main benefit of participating is an altruistic one to improve care for subsequent patients who suffer from rib injuries.

The PIS will provide clear details of the anticipated risks and benefits of taking part in the study. The risk and benefits of the study will be discussed with the participating sites as part of the process of inviting patients to take part and providing written informed consent.

22.1 Statement of indemnity

The necessary trial insurance is provided by the Sponsor. North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial. The PIS provides a statement regarding indemnity for negligent and non-negligent harm.

23 DISSEMINATION POLICY

The CI and TMG will establish a writing committee which will be responsible for preparing scientific reports of the study findings. The aim will be to publish a primary manuscript in an emergency medical journal, published as open access, with additional qualitative analyses described in specialty journals. Primary findings will also be presented at key meetings e.g. the Annual Conference of the Royal College of Emergency Medicine, the European Society of Emergency Medicine Congress.

We will complete a full report for the NIHR. If we determine a full trial is feasible, we will submit a grant proposal for the consideration of the NIHR at the end of the study.

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25 DOCUMENT HISTORY

Version Number	Version Date	Summary of Changes
1.0	16DEC2020	N/A – new document.
2.0	09MAR2021	Revisions following Research Ethics Committee (REC; England & Wales) review; Provisional Opinion.
3.0	30MAR2021	Revisions following Research Ethics Committee (REC; England & Wales) review; Favourable Opinion with Conditions.
4.0	04MAR2022	Update to the Clinical Trial Unit (CTU) information - from BRTC to BTC. The Bristol Trials Centre (BTC) was formed from the merger of the Bristol Randomised Trials Collaboration (BRTC) and the Clinical Trials Evaluation Unit (CTEU) and was granted registration as a single trials centre in Autumn 2021. The CTU involvement in this study has not changed, it is just a change of name and registration number. Update to investigator details: Chief Investigator substantive employer now noted and co-investigator (RK) job title and institute updated. Minor typographical updates, where appropriate. Minor clarification and update that patients with capacity can provide informed consent having read (*or* discussed) at least the Summary PIS. Furthermore, if they are unable to physically sign/mark a consent form (e.g. due to pain, frailty, visual impairment) then they may verbally give their informed consent in the presence of a witness. Minor clarifications to abbreviations and points of reference within the Safety Reporting section.

26 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

I also confirm that I will make the findings of the 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 and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../....../......

Name (please print):

....

Position:

....

Chief Investigator:

Signature: Date:

..../....../......

Name: (please print):

....

Statistician:

Signature: Date:

..../....../......

Name: (please print):

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APPENDIX 1. TABLE SUMMARY OF THE STUDY INVITATION AND CONSENT PATHWAYS

The table below outlines the documents and key processes required when inviting a potential participant to join the study and obtaining necessary consent (or equivalent advice for those who lack capacity). The potential pathways presented are:

1) Consent by patients in the Emergency Department
2) Participants losing capacity during participation in the study
3) Patients lacking capacity to provide consent in the Emergency Department
4) Participants regaining capacity during participation in the study

<table>
<tr><th></th><th colspan="2">ALL PATIENTS (ENGLAND, WALES AND/OR SCOTLAND)</th></tr>
<tr><td>1) CONSENT BY PATIENTS IN THE EMERGENCY DEPARTMENT</td><td colspan="2">a) <u>Invitation:</u> give patient the (1) Summary Participant Information Sheet (Summary PIS) and, where appropriate, the (2) full Participant Information Pack (e.g. patient has read the Summary PIS and requested further information and/or is suitably comfortable and able to read both documents at that time).
b) <u>Consent (if willing and eligible):</u> ask patient to complete the default online eConsent Form (or paper equivalent if online eConsent is not feasible).</td></tr>
<tr><td>Legal framework</td><td>PATIENTS IN ENGLAND AND WALES
Mental Capacity Act 2005</td><td>PATIENTS IN SCOTLAND
Adults with Incapacity (Scotland) Act 2000</td></tr>
<tr><td>2) PARTICIPANTS LOSING CAPACITY DURING PARTICIPATION IN THE STUDY</td><td>If a participant loses capacity during the study 30-day period then either a Personal (or, if not available, a Nominated) consultee will be approached about the patients’ continuing participation in the study, as described in <u>point 3</u>, below.
If a Consultee is not available or is unwilling, then the participant will be withdrawn from the study, but data already collected (up to the point of withdrawal) will be retained.</td><td>The Act does not refer to adults who lose capacity while taking part in non-CTIMPs in Scotland. Thus, we propose using a process equivalent for patients in England in Wales.
If a participant loses capacity during the study 30-day period then a legal representative should be approached about the patients’ continuing participation in the study, as described in <u>point 3</u>, below.
If a legal representative is not available or is unwilling, then the participant will be withdrawn from the study, but data already collected (up to the point of withdrawal) will be retained.</td></tr>
<tr><td colspan="3" align="right">Please continue over the page.</td></tr>
</table>

Legal framework	**PATIENTS IN ENGLAND AND WALES** *Mental Capacity Act 2005*	**PATIENTS IN SCOTLAND** *Adults with Incapacity (Scotland) Act 2000*
3) PATIENTS LACKING CAPACITY TO PROVIDE CONSENT IN THE EMERGENCY DEPARTMENT	Take reasonable steps to **seek an opinion (advice) from a Consultee** about whether the named patient (potential participant) would wish to be included in the trial or not. **PERSONAL CONSULTEE:** In the first instance, this should be from a **Personal Consultee** (i.e. the patient's partner, or a particular friend or carer who is not seeking renumeration for doing so or acting in a professional capacity). **a)** Invitation: Discuss/provide the (**1) Consultee Summary Information Sheet** and, where feasible and appropriate, the **(2)** further **Personal Consultee Information Pack.** **b)** Advice about whether the patient should be included, or not: If willing and agreeable: complete the **Personal Consultee Declaration Form (Verbal or In-Person version)** using default online eForm (or paper equivalent if online eForm is not feasible). **NOMINATED CONSULTEE:** If a Personal Consultee is not available or unwilling, then a **Nominated Consultee** (appointed by the local Principal Investigator) will be approached instead. **a)** Invitation: Discuss/provide the (**1) Consultee Summary Information Sheet** and, where feasible and appropriate, the **(2)** further **Nominated Consultee Information Pack.** **b)** Advice about whether the patient should be included, or not: If willing and agreeable: complete the **Nominated Consultee Declaration Form (Verbal or In-Person version)** using default online eForm (or paper equivalent if online eForm is not feasible).	Take reasonable steps to **obtain consent** on behalf of the patient who lacks capacity to do so themselves, from a **legal representative**: • **Welfare Guardian or Welfare Attorney,** or if not in place; • the **patient's nearest relative.** **a)** Invitation: Discuss/provide the (**1) Welfare Guardian or Attorney/Nearest Relative Summary Information Sheet** and, where feasible and appropriate, the **(2)** further **Welfare Guardian or Attorney/Nearest Relative Information Pack.** **b)** Advice about whether the patient should be included, or not: If willing and agreeable: complete the **Welfare Guardian or Attorney/Nearest Relative Consent Form (Verbal or In-Person version)** using default online eForm (or paper equivalent if online eForm is not feasible). **If a Welfare Guardian or Attorney, or Nearest Relative, is not available or unwilling**: there are no alternative provisions for a non-CTIMP study in Scotland and the patient will not be recruited into the trial.

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Adults with Incapacity (Scotland) Act 2000</th></tr>
<tr><td>4) PARTICIPANTS REGAINING CAPACITY DURING PARTICIPATION IN THE STUDY</td><td>If a participant regains capacity during the study 30-day period, then reasonable steps will be taken to obtain retrospective (recovered) consent from the patient when feasible.

a) <u>Invitation:</u> give patient the appropriate Recovered Capacity Participant Information Sheet.

b) <u>Consent (if willing and eligible):</u> ask patient to complete the appropriate default online Recovered Capacity eConsent Form (verbal or in-person version) (or paper equivalent if online eConsent is not feasible).

<u>If the patient does not wish to continue participation</u>: they will be withdrawn from the study. Permission will be sought to retain data already collected (up to the point of withdrawal), and to continue to access central medical records.</td><td>If a participant regains capacity during the study 30-day period, then reasonable steps will be taken to obtain retrospective (recovered) consent from the patient when feasible.

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