Study Title: A multicentre randomised controlled trial assessing the mortality, quality of life, and cost effectiveness of operative rib fixation plus supportive management versus supportive management alone for patients with multiple rib fractures requiring ventilator support.

Short title: The Operative Rib Fixation (ORiF) Study

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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TABLE OF CONTENTS

1. SYNOPSIS

Study Title	A multicentre randomised controlled trial assessing the mortality, quality of life, and cost effectiveness of operative rib fixation plus supportive management versus supportive management alone for patients with multiple rib fractures requiring ventilator support.	
Short title	The Operative Rib Fixation (ORiF) Study	
Study Design	Randomised controlled trial with registry embedded data collection	
Study Participants	Participants aged 16 years or older who have sustained multiple rib fractures and are suitable for surgical fixation.	
Planned Sample Size	532	
Planned Study Period	54 months	
	Objectives	**Outcome Measures**
Primary	• To assess differences in all-cause mortality between the intervention and control groups at 12 months. • To quantify and draw inferences from observed differences in quality of life over 12 months following surgery.	• All-cause mortality data. • EQ-5D-5L index with direct trial collection of primary outcome data

Secondary	• To compare patient reported pain and function over 12 months (measured in terms of struggling with breathing, difficulties with independence, anxiety about cosmesis, return to work and return to physical activity);
	• To compare the need for further intervention in addition to supportive management versus supportive management alone;
	• To compare length of stay (LOS) between the rib fixation with plates and screws in addition to supportive management versus supportive management alone;
	• To assess the cost-effectiveness of rib fixation with plates and screws in addition to supportive management versus supportive management alone;
	• To assess the generalisability of the findings from the randomised trial against the population registry data using a recent statistical approach.
		• Pain Visual Analogue Scale (VAS) and function-related questionnaire
		• From patient hospital records/TARN data
		  ○ Length of hospital stay
		  ○ Operative and standard care details
		  ○ Complications
		  ○ Further intervention
		  ○ Ventilator days
		• Health Resource Use questionnaire
		• TARN data for both randomised and non-randomised patients

2. ABBREVIATIONS

AIS	Abbreviated Injury Scale
ATLS	Advance Trauma Life Support
BOA	British Orthopaedic Association
BOAST	British Orthopaedic Association's Standards for Trauma
CI	Chief Investigator
CRF	Case Report Form
CRPD	Clinical Practice Research Datalink
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ICU	Intensive Care Unit
LOS	Length of Stay
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCTS	Society for Cardiothoracic Surgery
SOP	Standard Operating Procedure
TARN	Trauma Audit and Research Network

3. BACKGROUND AND RATIONALE

Injuries from trauma are a leading cause of death in the UK. Blunt injury to the chest wall due to falls, road traffic accidents and physical assaults, commonly result in fractured ribs, contusion or laceration to the underlying lung, and occasionally more severe injury to the heart or main blood vessels. Injuries to the chest wall can directly compromise a patient's ability to breathe. When patients have compromised chest wall mechanics they suffer from paroxysmal ventilation, commonly known as "a flail chest" (1).

Chest injuries are one of the commonest causes of death following trauma and 16% of patients suffering major injuries have rib fractures (2). They are common in young patients suffering from high energy trauma (such as road traffic accidents) and also in the elderly where rib fractures are the second most common fragility fracture in the National Health Service (NHS). Both populations carry a high morbidity and mortality despite developments in supportive management (3). Care of patients with chest wall injuries (including both traumatic fractures and fragility rib fractures) represents a major financial and

social burden to the NHS. Patients often require admission to Intensive Care Units (ICUs) and require specialist nursing, and ventilatory support. Compromised respiratory function (usually caused by three or more fractured ribs), can lead to pneumonia and even death. For those who survive, the rehabilitation can be long and involved.

Previously patients have been mostly managed conservatively, with supportive management consisting of pain control, specialist physiotherapy, invasive and non-invasive assisted ventilation as required and daily multidisciplinary review. More recently there has been increasing use of surgery to manage rib fractures (rib fracture fixation), particularly in patients with multiple injuries. This is in addition to the routine conservative supportive management (2).

Early indications from the Trauma Audit and Research Network (TARN) registry show surgical rib fracture fixation leads to a decrease in mortality in the more severely injured (4). TARN data also shows patients recover quicker and have better health outcomes with rib fracture fixation plus supportive management (4). The addition of surgery for these patients increased in frequency by 320% between 2014 and 2015 (2). This is despite the lack of rigorous evidence, or a health economic analysis to prove its efficacy.

Existing Evidence

Published comparative studies evaluating surgical fixation are limited to three small randomised trials, and one matched observational study (5-8). These all indicate a reduction in mortality and health economic benefit but suffer from high risks of bias (4). Only one of the three randomised studies evaluates fixation with a plates and screws approach (5). The other two studies evaluated different surgical approaches (using Kirshner wires and a rib crimp system). Outcomes from these studies show some anecdotal evidence that stabilisation of the chest wall through fixation of the ribs is beneficial (4). Benefits in terms of a reduction in complications (such as pneumonia) and length of stay were identified. Mortality data was equivocal though a potentially practice shifting benefit with rib fixation seen as plausible.

The observational study, with an analysis of matched patients, found a substantially reduced mortality and better quality of life outcome at 30 days in patients who had plate and screw rib stabilisation (8). This is supported by evidence from the Canadian National Trauma Databank (9) who observed a significant improvement in mortality in those patients treated with operative stabilisation of their flail chest injuries (odds ratio of 0.16 in favour of operative stabilisation) (9). The National Institute for Health and Care Excellence (NICE) issued guidance in 2010 allowing rib fixation in patients with a flail chest, however they noted the limited evidence, and stopped short of recommending the treatment for all operable patients.

Concerns identified as important by patients in qualitative research, such as long recovery times, treatment associated complications and the risk of death have not been addressed sufficiently in the previous research and require further consideration in future research (10).

Health economic evaluation from the USA suggests surgical costs of $23,682 and non-operative treatment costs of $8,629 per case (11). Improved outcomes from surgical management gave an incremental cost-effectiveness ratio of $8,577/QALY (11). If costs are comparable, this would equate to an annual cost to the NHS for chest injury treatment in the range of $112 million (all non-operative) to $307 million (all operative) based on the 13,000 patients who presented through the major trauma

network with a chest injury due to a moderate or severe traumatic injury in 2016 (2). This study, although encouraging, again relies on poor quality data with high risks of bias.

The small size, potential lack of generalisability and the risk of bias in these previous studies cannot be overlooked; only a large multicentre trial can likely provide a finding which would be considered widely convincing. A recent Cochrane review also specifically recommends further studies evaluating rib fixation which are large enough to assess mortality(12).

Indications for Surgical Rib Fracture Fixation

Clinical indications for rib fracture fixation is varied. Our recent surveys of major trauma centres (MTCs) across the UK, a Cochrane review, NICE guidance, the systematic review, and the British Orthopaedic Association's Standards for Trauma (BOAST) highlight this variation (2, 4, 12, 13). This issue is caused by the diverse interpretations of what defines a "flail chest" in the first instance (12). Guidance from the BOA and the Society for Cardiothoracic Surgery (SCTS) applies to all patients with blunt chest wall trauma. The guidance provides audit standards, and stipulates that patients with a chest wall injury should be managed as part of an agreed care pathway, including "Consider surgical stabilisation for patients with severe chest wall injuries including flail chests, injuries causing respiratory compromise or where pain control cannot be achieved".

A flail chest can be caused by a multitude of pathologies, and in the presence of other major injuries (12). However definitions of flail chest vary and are inconsistently applied (14). A recent Cochrane review defines a flail chest as "a segment of chest wall that moves paradoxically with respiration relative to the rest of the chest wall" (4, 12, 15) . Further to this through a consensus process in 2015, involving workshops, surveys, audits and a final consensus held by the BOA, national audit standards were agreed and published as BOAST-15 (16).

The potential risks of rib fixation surgery in severely injured patients needs to be weighed against other treatment goals, such as improving ventilation and reducing complications like pneumonia, death, and the potential to improve quality of life.

Evidence why this research is needed now

Despite being high on the national agenda, and a question of clear clinical, patient, and societal importance, there is a paucity of robust and relevant evidence to either support or halt the growth of rib fracture fixation. Additionally, very little evidence exists on the most recent approach to rib fixation with plates and screws which is the intervention increasingly used in the NHS and supported by NICE guidance (12). Existing evidence, despite its limitations, suggests benefits including the possibility of a substantial practice shifting mortality benefit. Data from all moderately and severely injured patients in England is now reported as part of the TARN registry. By utilising this registry data, the aim of this trial is to address the gap in evidence on treatment of multiple rib fractures with plate and screw fixation in addition to supportive management versus only supportive management.

4. OBJECTIVES AND OUTCOME MEASURES

The study will assess what the clinical management pathways for these patients within the first 72 hours of their injury.

This study has co-primary objectives with both patient mortality and quality of life as the focus. All data will be collected over a period of 12 months (see Appendix B for time points).

Objectives	Outcome Measures
• To assess differences in all-cause mortality between the intervention and control groups over 12 months. • To assess and draw inferences from observed differences in quality of life at 12 months following surgery.	• All-cause mortality dataEQ-5D-5L
• To compare patient reported pain and function over 12 months (measured in terms of pain, struggling with breathing, difficulties dressing, anxiety about health state and return to physical activity); • To compare the need for further intervention in addition to supportive management versus supportive management alone; • To compare length of stay (LOS) between the rib fixation with plates and screws in addition to supportive management versus supportive management alone;	• Pain Visual Analogue Scale (VAS) and Function-related patient questionnaire • From patient hospital records/TARN data o Length of hospital stay o Operative and standard care details o Complications o Further intervention o Ventilator days o CT images (all groups) o X-ray images (surgical group only)
• To assess the cost-effectiveness of rib fixation with plates and screws in addition to supportive management versus supportive management alone; • To assess the generalisability of the findings from the randomised trial against the population registry data using a statistical approach.	• Health Resource Use questionnaire • TARN data for both randomised and non-randomised patients

4.1. Primary Outcome Data Collection

The study will collect co-primary outcome measures.

Data on all-cause mortality will be collected from the sites on a monthly basis.

Quality of life data will be collected via patient reported questionnaires, EQ-5D-5L over 12 months. Baseline quality of life will be collected retrospectively at 30 days post-randomisation.

4.2. Secondary Outcome Data Collection

Secondary outcomes include clinical and patient reported outcomes as well as a cost-utility analysis comparing surgical fixation and supportive management versus supportive management alone. The secondary outcome measures include:

4.2.1. Patient Reported Questionnaires

A VAS will be used to measure patient reported pain.

A patient reported function questionnaire has been developed based on previous qualitative research. This focuses on the questions most pertinent to patient function. The domains included address the themes of struggling with breathing, difficulties with independence, anxiety about cosmesis, return to work and return to physical activity. These questions have been developed in conjunction with our patient group and are based on previously undertaken qualitative work.

4.2.2. Patient Hospital Records and TARN Data

Data on the care the participant receives whilst in the hospital will be recorded in the TARN registry. Data on the number of days the participants are on a ventilator for, the length of stay (LOS) in hospital, further interventions and return to theatre will be collected. In addition any requirement for respiratory support will be collected. All this information will also be recorded on trial-specific Case Report Forms (CRFs) in order to assess the feasibility of imbedding a trial within a registry for this patient population.

Data on the occurrence, date and cause of death will be collected from site hospital records (NHS Spine) and by using available public data (for example the Office of National Statistics(ONS)).

4.2.3. Radiology and X-ray Images

Diagnosis is made using axial CT scan images. These will be collected for both groups, including their verified reports to confirm diagnosis, and other chest injuries.

Imaging conducted post operatively will be collected for all patients who have rib fixation surgery to assess the fixation (positioning and hold). This is routine imaging, completed post-operatively. The study will collect all images taken up to 8 weeks post-surgery. The images will be used to check for and confirm complications related to the surgery whilst also used in the surgical procedure validity assessment.

4.2.4. Health Resource Use

To assess and compare the cost effectiveness of both treatment arms, data on the use of health resources post-discharge from in-patient care and during community rehabilitation. The EQ-5D will be recorded in patient reported questionnaires. Although EQ-5D-5L will be reported as the primary outcome as it is more sensitive and reduces the ceiling effects, the EQ-5D-3L will also be collected in this study as the 5L valuation set is not recommended for use by NICE yet (17) and the response level ‘confined to bed’ in the 3L mobility domain (versus ‘unable to walk about’ in the 5L) might be more relevant to the patients here.

5. STUDY DESIGN

ORiF is a pragmatic, multicentre two-arm parallel group (1:1) randomised trial nested within a population registry. Incorporated within the trial is a check of the recruitment and viability (internal pilot). The trial will involve 15 trauma centres/units across the UK. The trial will compare the initial management for patients with severe chest wall injury. A clinical and cost effectiveness evaluation will be undertaken up to 12 months following treatment, with data collection at 6 and 12 months. Primary data collection will be collected both by the study team, with supplementary collection of data through the TARN network as part of standard of care (see Flowchart in Appendix A).

5.1. Study Setting

The study will be conducted in fully capable Major Trauma Centres/Units across the UK that can offer ICU, in-patient wards, outpatients and theatres sufficient to deliver supportive management according to the accepted clinical standard and surgical fixation.

5.2. Embedded Registry Data Collection

The TARN national registry will be used to collect core clinical data, process measures including admission details and patient demographics and short-term secondary outcomes. The data collected from TARN will be compared to the trial data collected in CRFs in order to assess the feasibility of imbedding a trial within a registry for this patient population.

5.3. Internal Pilot

The internal pilot will take place in 6 centres initiated in a staggered pattern over a period of 6 months (26 recruitment months). The overall recruitment target for this period will be 52 patients (centre recruitment target rate of two patients per month). The aim of the internal pilot will be to assess the recruitment strategy, and modify as appropriate. In the more extreme scenario of very low recruitment (15 patients or less), the viability of the trial will be reconsidered with the funder. During this initial recruitment period, the realistic number of eligible and recruited patients in the trauma centres over the course of 6 months will be closely monitored and centres provided with regular individualised feedback. Screening logs will be kept at each centre to determine the number of patients assessed for eligibility and reasons for any exclusion. Rates of consent withdrawal will also be recorded. The initial 6 centres will also be used as a basis for testing the procedures for consenting, and collecting outcomes, including linkage to the TARN registry measures required for the economic evaluation.

Frequent change in clinical management from supportive management to operative rib fixation is not considered a threat to study completion or a problem for analysis. The need for surgery, based on the standardised criteria outlined in section 8.1, would indicate failed management and will be an outcome measure in itself. Obviously, it will not be possible for patients to change from operative rib fixation to supportive management alone once surgery has been performed. However, it is possible that some patients may be deemed to be clinically inappropriate for surgery after randomisation. Both these situations, and reasons for change in strategy, will be recorded on the clinical in-patient case report form.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

The target population is patients with multiple rib fractures suitable for surgical fixation. Patients with either isolated chest injuries or polytrauma including chest injury will be eligible. This is in-line with the nationally agreed BOAST guidance agreeing patient suitability for rib fixation (16).

6.2. Inclusion Criteria

Patients will be suitable for inclusion in the study if they present with multiple (3 or more) rib fractures suitable for surgical repair and one or more of the following:

- Clinical flail chest
- Respiratory difficulty requiring respiratory support
- Uncontrollable pain using standard modalities

6.3. Exclusion Criteria

Patients will be excluded if:

- Aged under 16 years
- Thoracic injury requiring emergent operative or interventional radiology
- Cannot be operated on within 72 hours as deemed unfit for surgery

7. STUDY PROCEDURES

7.1. Recruitment

Patients presenting with an acute chest injury are generally admitted to the hospital via a 'trauma call' from the emergency department either as the result of a 'pre-alert' from the ambulance service or on arrival. All adult patients presenting to the hospital via a trauma call will be screened by the clinical care team to check they are eligible to participate. The patient, or consultee, in conjunction with their surgeon, will decide if they are eligible to take part in the trial and will be referred to the research team for recruitment.

Patients who are able to give informed consent preoperatively will be approached and recruited by a member of the research team.

Patients who are unconscious or lacking ability to process information, will be recruited to the study under consultee agreement. Patient consent will not be obtained prior to randomisation and the start of the allocated treatment arm, but a consultee will be approached to provide consult for entry to the trial. A consultee will be the next of kin, if available, or a medically trained clinician independent to the trial. At the first appropriate time if the patient has regained capacity, the research team will provide written and verbal information about the study. Patients will be given the opportunity to ask questions and discuss the study with their family and friends. They will then be asked to provide written consent to continue with the study and the required follow up.

Information on the number of patients screened for recruitment and the number randomised will be collected throughout the trial to assess: the main reasons for patient exclusion; the number of patients unwilling to take part; and the number of patients who withdraw post-treatment.

Recruitment will run for a period of 30 months.

7.2. Informed Consent and Consultee Declaration

The participant or consultee must personally sign and date the latest approved version of the Informed Consent Form (ICF)/Consultee Declaration Form before any study-specific procedures are performed.

An information sheet about the trial will be provided in the first instance to the patient or consultee. Specifically, the responsible doctor will explain that the patient will receive the usual emergency treatments for their injuries but in addition to these, the patient will be enrolled in a research study that aims to improve the treatment of patients with traumatic rib fractures. It will be explained that the study is being undertaken to see if surgical treatment as well as standard care will help improve outcomes in patients.

The urgent nature of the treatment limits the ability to have informed discussions with patients and personal consultees, therefore limited time is available to consider study participation. However, as much time as clinically possible within each patient situation will be given. Written patient informed consent/consultee declaration will be obtained by means of a participant/consultee dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the patient consent/consultee declaration must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed ICF/Consultee Declaration Form will be given to the participant/consultee. The original signed form will be retained at the study site.

Informed consent from participants who re-gain capacity (initially entered in the study under consultee declaration), will be obtained at the earliest opportunity. This will involve signing an ICF which indicates they consent to continue in the study. Further detailed information will also be provided to the participant/consultee stating no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

If a patient or consultee declines to agree for continuation at this stage, his/her wishes will be respected. For any patient who was included but did not regain full capacity, consent to continue will be sought from a relative or other appropriate representative. If consent is not given to continue within the study, only treatment-related data routinely collected by TARN will be used and included in the final study analysis.

7.3. Randomisation

Randomisation will be performed using a web based automated computer generated minimisation with treatment groups balanced for: age, gender, polytrauma, mechanical ventilation and study centre. The minimisation algorithm will incorporate a random twist. Other than the allocated intervention, both

groups will be followed-up in the same way to exclude bias beyond procedures necessary for the allocation treatment. Neither participants nor operating surgeons can be blinded to receipt of the surgery. 532 patients will be recruited from up to 15 NHS orthopaedic trauma centres across the UK over a period of 3 years. The trial will incorporate an "internal pilot" recruitment assessment.

The allocation sequence will be generated by the trial statistician and will be programmed into the OCTRU computer randomisation system called Registration/Randomisation and Management of Product (RRAMP). The research team at each site will conduct the randomisation via secure log-ins to the web-based system.

7.4. Baseline Assessments

Baseline assessments will not be possible on all participants, due to the nature of the injury and the recruitment procedure. Patients are commonly incapacitated and unable to complete patient reported questionnaires. However, demographics and details required for randomisation will be collected.

Baseline health related quality of life data is also required in order to make a valid comparison and analysis. A proportion of patients who are registered with a GP practice which is part of the Clinical Practice Research Datalink (CPRD) database will have both full medical records preceding the injury. The CPRD will be queried in these patients to provide additional information on patients' background medical history. Health related quality of life questionnaires will be completed retrospectively within the index admission. This method has been used in previous studies involving trauma related patient populations (18). It is anticipated some patients will re-gain capacity by 30 days post-randomisation, and some will die. This time point will be used for patients to retrospectively recall their pre-injury health-related quality of life. This will be recorded on the EQ-5D.

7.5. Follow Up Assessments

Data on the intervention and follow up data will be collected via combination of methods:

- Patient reported questionnaires/patient reported outcome measures will be sent directly to the patient, and
- Data from the registry (TARN)
- From assessments during routine clinical appointments (i.e. radiological imaging).

The quality of life primary outcome will be collected directly from patients. The quality of life questionnaire (EQ-5D) from questionnaires sent directly to patients from the central study team in Oxford (via email or post, according to patient preference).

The all-cause mortality data will be collected directly from sites on a monthly basis and cause of death data from sites and available public data.

The TARN registry will be used to collate data on standard in-patient clinical treatments and also to process secondary outcome measures and other details relating to the injury. This includes demographic data, data related to the injury and details of the intervention including timings. Compliance to allocation will be collected using a separate bespoke CRF to supplement the data recorded within TARN.

7.5.1. Patient Reported Outcome Measures (PROMs)

At 90 days and again at 6 and 12 months post-randomisation, participants will be sent a questionnaire via email or post (whichever method they indicate a preference for). These questionnaires will include:

- Patient-reported questions on function
- Pain Visual Analogue Scale
- EQ-5D-5L
- EQ-5D-3L
- Health-related resource use

7.5.2. Complications

Patient reported questionnaires will ask if participants have returned to see a health care professional or be readmitted to hospital in relation to complications with their rib fractures and treatments. The central study team will follow up any complications reported by patients with the research team at the trial site. Further details will be collected and recorded on the Complications CRF. Sites will also conduct regular routine checks on their patients to check for readmissions related to their participation in the study.

7.5.3. X-rays

Patients randomised to operative fixation plus standard care will have routine x-rays around 6-8 weeks post-discharge. These images will be collected centrally and used to review for or confirm complications and also in the assessment of surgical fidelity.

7.6. Discontinuation/Withdrawal of Participants from Study

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow up and data collection. Each participant has the right to withdraw from any aspect of the trial at any time. In addition to participant self-withdrawal, an investigator may decide to withdraw a participant if considered necessary for a clinical reason. For those patients withdrawing from the trial after written consent/agreement has been obtained, data collected up until the point of withdrawal will be included in the final analysis.

7.6.1. Withdrawal or Change of Treatment

If patients have been randomised into the study and then do not continue with the treatment regime, either due to self-withdrawal or on the recommendation of their clinician, the reasons for withdrawal or change in treatment will be recorded if available and sites should explain the importance of participants remaining on the trial follow up. If participants are willing, they will be followed up accordingly.

Withdrawal from Follow Up

Participants may withdraw from the follow-up regime or from the trial altogether. If so, their decision should be recorded in the CRF and medical notes and only data up to the point of

withdrawal will be collated and analysed accordingly. The patients will be encouraged to discuss treatment options with their clinician.

In the event of discontinuation or withdrawal from the trial the reason will be recorded on the CRF. Withdrawn participants will not be replaced as withdrawals and loss to follow-up has been accounted for in the estimated sample size. Analysis will be performed on an as randomised irrespective of compliance with treatment allocation basis.

Participants wanting to withdraw from the follow up will be asked to consider allowing the continuation of the collection of their related TARN data.

Definition of End of Study

The end of trial is defined as 45 days after the final participant questionnaire has been delivered, and all the data has been entered, queries resolved, analysis completed and dissemination undertaken.

8. INTERVENTIONS

This study compares two routinely used strategies for management of patients with multiple rib fractures within the first 72 hours of injury;

- Operative rib fixation plus supportive management and
- Supportive management alone

Both interventions are routinely available within the NHS. All participating study centres are already offering care in line with the national consensus statement and BOAST-15 audit standards (16). The study design is pragmatic in that the delivery of the intervention will reflect regional variations and differences in service provision within the participating centres and different major trauma networks. To give a realistic reflection of how each management strategy performs within the NHS, we have defined the key components to each intervention which need to be standardised.

8.1. Supportive Management

All patients, weather randomised to surgery or not will receive supportive management. This will be delivered by a multi-disciplinary team comprising of surgeons, physiotherapists, pain management specialists, intensive care doctors (if appropriate). As part of the centre selection process, an audit of facilities and documentary evidence of a patient care pathway that reflects standards of care set by the study will be required. Supportive management in the study involves the following aspects:

During admission through the accident and emergency department:

- During admission, patients will be managed by a consultant led trauma team in a multidisciplinary multispecialty manner.
- Resuscitation using a modern Advance Trauma Life Support (ATLS) pathway including the use of new technologies (e.g. trauma CT, tranexamic acid and thromboelastography).
- Associated thoracic injuries (including haemothorax, respiratory compromise or pneumothorax) will be managed immediately within the resuscitation room.

- Early contrast CT scanning should be obtained including 3D surface rendered images of the thorax to facilitate accurate diagnosis.
- Pain should be managed as appropriate with an agreed protocol including access to neuraxial and opioid analgesia as appropriate.
- A chest drain should be inserted if required for patients presenting with a moderate heamothorax or pneumothorax. These should be a large bore trauma chest drain inserted using a sterile open technique, by a qualified doctor.
- Ongoing care should include management in a multidisciplinary team including specialist consultant-led surgical, intensive care, pain management and physiotherapy teams and be in a designated trauma ward or intensive care facility.

During in-patient admission:

- Patients should be reviewed daily by the medical team and receive multidisciplinary care including physiotherapy, pain management and trauma surgeons. This should include intensive care review in the case of respiratory compromise.
- Routine management of chest drains, routine radiographs in the case of pneumothorax, haemothorax or chest drain removal and physiotherapy should be undertaken according to local protocols.
- Patients should have a comprehensive review prior to discharge, including a rehabilitation prescription and in the case of repatriation to a trauma unit prior to discharge home, the locally agreed discharge and repatriation network protocols should be utilised.
- Ongoing care from a rehabilitation consultant with an interest in traumatic injuries should be available as appropriate and continued care from surgical, pain management and specialist respiratory physiotherapy teams should be available.

The progress of patients who are randomised to supportive management alone will be monitored by the multidisciplinary team overseeing their care. If certain circumstances arise the clinicians may decide the patient requires operative rib fixation. These circumstances include, but are not limited to:

- Failure to wean using supportive measures
- Secondary ventilatory support following weaning
- Persistent or ongoing ‘air leak’ secondary to parenchymal damage

The reasons for moving to operative rib fixation will be recorded appropriately in the in-patient case report form and details of the surgery documented.

It is anticipated far fewer participants will move from operative to non-operative treatment. Those who do will likely do so due to an acute deterioration rendering the participant unsuitable for surgery.

8.1.1. Fidelity Assessment of Supportive Management

To assess fidelity and content of standard care the following information will be collected and reviewed:

- Which neuraxial analgesia was used:
    - Intercostal blocks
    - Epidural
    - Paravertebral blocks
- When the patient received their pain management review
- Which physiotherapy interventions were used:
    - In person physiotherapy
    - Incentive spirometry
    - Access to specialised physiotherapy such as Intermittent Positive Pressure Breathing ('The Bird')

Each participating site will have written guidelines on what their standard care involves. These will be collected and reviewed as part of site feasibility assessment. The standard care given to both arms needs to be the same within each site. If the written guidelines indicate there is no pain team review available and no physio involvement, the site may not be a feasible participant.

8.2. Surgical Fixation

All patients randomised to surgical fixation will also receive supportive management as detailed above. Surgery will be undertaken within 72 hours of admission, measured from the date/time of admission to the date/time of surgery. The operation is delivered unusually by a range of different specialities, with dual consultants operating in some cases. Specialities in the UK currently undertaking rib fracture fixation include Orthopaedic surgeons, Thoracic surgeons, Major Trauma surgeons, and Emergency surgeons with each unit having its own strategy for provision of surgical care. In every unit in the country cases are admitted either under a Major Trauma team or Orthopaedic trauma team routinely, although in some centres secondary transfers may be directly under thoracic surgery.

Prior to surgery patients will have a multidisciplinary review including surgical and anaesthetic review. Patients will be optimised for surgery following a pre-operative assessment, and surgery will be undertaken on a planned list by a surgical, anaesthetic and theatre team trained in rib fixation for traumatic chest injuries. Local protocols for antibiotic prophylaxis, anaesthetic care and peri-operative care will be followed.

The operative intervention will be compliant with NICE guidance (IPG361):

- The patient will be under general anaesthesia.
- An open approach via an incision is made over the rib fractures to be treated.
- The fractured ribs are reduced under direct vision.
- The affected ribs are stabilised using a metal plates or splints, fixed with screws. The study will allow fixation with 'rib splints' which are a plate construct, fixed with a screw that is inserted within the intra-medullary canal of the rib.
- Rib plates or splints will be contoured to fit the rib, applied to the outer surface.
- Lung and vascular injury will be addressed as appropriate at the time of surgery.
- Fracture reduction technique, and numbers of fractures reduced will be left to the discretion of treating surgeon.
- Routine x-rays at 6-8 weeks post-discharge.

There are a variety of constructs available to stabilise the chest wall, however as NICE guidance notes the risk of complications includes migration of the metalwork, and they advise that Kirschner wires should not be used alone. Accordingly, such an approach will not permitted in this study.

Following surgery patients will be managed as per supportive management.

To implement and deliver a standardised surgical technique, materials from rib fixation training courses will be utilised in site training and initiation visits.

In patients with bilateral chest injuries treatment of one or both sides will be at the discretion of the operating surgeon. The patient will be treated as a single participant. In some cases it is anticipated that these interventions will need to be staged. All surgical rib fixation procedures will be recorded accordingly.

8.2.1. Fidelity Assessment of Operative Rib Fixation

To assess fidelity and standardisation of the surgical intervention for each case the study will utilise details provided on the following documents:

- An operative CRF including operative technique, complications and implants used.
- The operative record on TARN
- Post-operative x-rays to assess the fixation
- Images taken up to 8 weeks after surgery to assess the fixation

9. SAFETY REPORTING

The study involves routine standard care for the management of patients with multiple rib fractures. There is no additional risk to patients. They will either have standard care with operative rib fixation or standard care alone. Patients will be informed of the standard risks associated with the anaesthetic and surgical fixation, as well as the risks associated with standard care.

All deaths will be recorded on a Death Notification Form. Complications that local clinicians deem associated with this patient population and the trial treatments will be recorded on a Complications Form. Examples of expected complications include, but are not limited to: pneumothorax, haemothorax, requirement for secondary ventilator support following extubation, loss of metalwork stability, wound infection etc.

Complications will be periodically reviewed by the DSMC and any unusual increased patterns of serious adverse events (i.e. complications which are serious) compared to what is expected for such patients and interventions will be notified to the REC.

9.1. Reporting Procedures for Unexpected Serious Events

A complication that is life-threatening occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of life-threatening, related and unexpected events will be submitted within 15

working days of the Chief Investigator becoming aware of the event, using the Health Research Authority (HRA) report of serious adverse event form (see HRA website).

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

All statistical analysis shall be carried out by the Statisticians based at the Centre for Statistics in Medicine, University of Oxford. Study statistical analyses will follow a statistical analysis plan agreed in advance by the Trial Steering Committee (TSC). A single set of final analyses will be performed at the end of the follow-up.

Statistical significance will be at the 5% level with corresponding confidence intervals derived. Under the principal analyses, all participants will be analysed according to their allocated group irrespective of compliance with treatment allocation. Principal analyses will be on an "as randomised" basis retaining participants in their randomised allocation groups irrespective of compliance to the allocation. The principal analyses will also be carried out on a complete case basis with sensitivity to missing data explored for the primary outcome. Analyses will be carried out in Stata software version using the newest version available at the time of analysis (currently 15.1) (19). An independent Data Monitoring Committee (DMC) will meet early in the course of the trial to agree its terms of reference and will review confidential interim reports of accumulating data. No formal stopping rules are accounted for in the sample size and accordingly no formal interim analyses are planned.

A separate analysis will assess the consistency of the randomised trial finding to the wider registry TARN population (5000+ patients) both informally in terms of population characteristics and also consistency of estimates using propensity score weighted analysis(20).

10.2. The Number of Participants

Meta-analyses of two small RCTs, our observational study with matched groups, and TARN registry data suggest a large and potentially practice shifting (5-11% absolute) reduction in short term (30-90 day) mortality is realistic for surgery over only supportive management.(5-8) To detect a target mortality difference of 7% (10 to 3%) at 90 day with 2-sided 5% significance level and 90% statistical power, 532 participants (35 events) will be required (log-rank test). 10% was the observed 90 day mortality in the TARN registry data (2014-16) for this patient population receiving supportive management. Mortality is routinely collected within TARN system and by the ONS, therefore anticipated loss of data is negligible. 532 participants is also sufficient for the co-primary outcome, EQ-5D-5L, based upon a target mean difference of 0.09 (an important difference for EQ-5D-3L)(21)**,** SD of 0.3, at 90% power and 2-sided 5% significance level, allowing for 12% missing data (the zero value will be used for those who died).

10.3. Analysis of Outcome Measures

The co primary outcome measures (All-cause mortality and EQ-5D-5L) will be compared using a Cox and linear regression model (respectively) with adjustment for the minimisation variables. Secondary outcomes will be analysed using generalised linear multilevel models with adjustment for minimisation and baseline variables as appropriate. Exploratory subgroup analyses will explore the possible treatment

effect modification of clinically important factors (age, gender, polytrauma and mechanical ventilation), through the use of treatment by factor interaction, and will be interpreted cautiously. The impact of missing data and non-compliance will also be explored in sensitivity analyses using appropriate methods(22) (e.g. the rctmiss Stata command for assessing the impact of missing not at random for EQ-5D-5L using a pattern mixed-model based approach)(23), and complier average causal effect (CACE) type approaches respectively(24). Secondary unadjusted analyses on all-cause mortality and EQ-5D-5L will also be carried out log-rank and t- tests respectively.

10.4. Health Economic Analysis

An economic evaluation will be integrated into the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective (25). Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 12 months post-randomisation. At 6 and 12 months post-randomisation, trial participants will be asked to complete economic questionnaires profiling hospital (in-patient and outpatient) and community health and social care resource use and, for the purposes of sensitivity analysis, out-of-pocket expenditures and costs associated with lost productivity. Unit costs for health and social care resources will be derived from the latest local and national sources (26).

Health-related quality of life will be measured at discharge, 30 days (retrospective baseline), 3, 6 and 12 months post-randomisation using the generic EuroQol EQ-5D. As per the NICE position statement, the responses to the EQ-5D-5L will be converted into multi-attribute utility scores using an approved “cross-walk” to the three-level instrument and its established utility algorithm for the UK, using the mapping function developed by van Hout et al (27).

The economic evaluation will take the form cost-utility analysis expressed in terms of incremental cost per quality-adjusted life year (QALY) gained. Alongside the conventional cost-utility analysis, a cost-effectiveness of rib fixation with plates and screws plus supportive management versus supportive management alone, expressed in terms of incremental cost per number of deaths prevented in patients with multiple rib fractures, will be conducted. Both the cost-utility analysis and cost-effectiveness analysis will be presented in terms of an incremental cost effectiveness ratio (ICER = $\Delta C/\Delta E$).

Deterministic sensitivity analysis (i.e. one-way sensitivity analysis) will be performed to explore the effects of extending the study perspective (i.e. societal perspective) and decision context as well as the impact of missing data and using the EQ-5D-3L on the ICERs. Impact of missing data will be explored in sensitivity analyses using appropriate methods (e.g. the rctmiss Stata command for assessing the impact of missing not at random for EQ-5D-5L using a pattern mixed-model based approach or the ice Stata command for assessing the impact of missing at random using a multiple imputation approach). Results from the one-way sensitivity analysis will be presented in Tornado diagrams. In order to assess sampling (or stochastic) uncertainty on the ICERs and varying levels of willingness-to-pay for an additional QALY, probabilistic sensitivity analysis (PSA) will be performed. Results from this PSA will be presented in cost-effectiveness acceptability curves (CEACs) which will be generated via non-parametric bootstrapping. CEACs will also be constructed using the net benefits approach, in which ICER is ‘linearised’ by the addition of the cost-effectiveness or willingness-to-pay threshold, in order to represent the uncertainty associated with results from the health economic analysis (28).

11. DATA MANAGEMENT AND SHARING PLAN

A Data Management and Sharing Plan will be produced for the trial and will include reference to confidentiality, access and security arrangements. All data will be processed in accordance with data protection rules. Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

All trial data will be collected on trial specific documents, for example questionnaires and case report forms (CRFs). All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. Participant identifiable data will be stored separately from study data and in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford and authorised personnel.

On completion of the study, and with appropriate participant consent, fully anonymised data may be shared with other organisations at the behest of the funder. All requests for the use of the data from the ORiF study will be approved by the CI, TMG and where necessary the TSC. A data request form should be completed detailing the decision as to whether the request is accepted. In cases where individual site data is requested, only summary data would be provided with caveats for dissemination, to emphasise that trial data should be interpreted as a whole.

12. QUALITY ASSURANCE PROCEDURES

The clinical trials unit (CTU) conducted a risk assessment prior to the study starting. Issues raised have been addressed within the final protocol and procedures have been planned to monitor the ongoing risks of the trial. A risk proportionate approach will be utilised within this trial and the trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Central monitoring of trial procedures will be imbedded into the trial conduct and management. The trial will be subject to audit by the Trial Manager, according to OCTRU's Audit Programme. The trial will also undergo a process of review before it is granted the green light to begin recruiting patients.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number, on all study documents and any electronic database. The participant ID number will be linked to their NHS number and their TARN ID. This is required as we collect and share data from the NHS and TARN directly. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the General Data Protection Regulation (GDPR) Data Protection.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

13.7. Other Ethical Considerations

The ORiF study involves obtaining consent in an emergency situation. The nature of the injury means patients may be operated on immediately or are allocated to the next available trauma operating list. The urgent nature of the treatment limits the ability to have informed discussions with patients and personal consultees. Some patients may be unconscious or have reduced levels of consciousness and many will be given strong analgesia. Therefore, many patients will lack capacity to provide informed consent before being entered into the study. Conducting research in an emergency setting with incapacitated patients is regulated by the Mental Capacity Act (MCA) 2005. The ORiF study will adopt a dual consent process. This is well embedded within many trauma trials and we do not anticipate additional risks to the patients (29). The dual consent process involves:

- Patients consented pre-intervention (both arms): Patients who are able to give informed consent preoperatively will be approached and recruited by a member of the research team.

- Patients consented post-intervention (both arms): Patients who are unconscious or lacking ability to process information, will be recruited to the study under consultee declaration. Patient consent will not be obtained prior to the start of the intervention, but a consultee will be approached to provide agreement for entry to the trial. A consultee will be the next of kin, if available, or a medically trained clinician independent to the trial. At the first appropriate time when the patient has regained capacity, the research team will provide all the study information.

Patients will be given the opportunity to ask questions and discuss the study with their family and friends. They will then be asked to provide written consent to continue with the study.

In instances where patients do not regain capacity, the consultee agreement will need to be re-confirmed for the patient to continue on the study. In instances where patients do not re-gain capacity and a nominated consultee provided initial agreement for participation in the study, efforts will be made to find a personal consultee. It will be clearly stated from the time the consultee is first approached that their agreement for the patient's participation can be withdrawn at any time.

An application for ethical and HRA approval will be made through the IRAS system in the pre-funding phase. Guidelines and corresponding procedures from the devolved nations will also be considered when implementing the consent process.

14. FINANCE AND INSURANCE

14.1. Funding

The study is funded by the National Institute of Health Research, Health Technology Assessment Programme (Ref 16/61/10). Funding will be managed by the Sponsor, Nottingham University Hospitals NHS Trust.

14.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If participants are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

15. PATIENT AND PUBLIC INVOLVEMENT

We will make the study information available on the NIHR, University (Nottingham and Oxford), and study website, including progress and results of the study. A study-specific Patient Advisory Group will lead on the dissemination of the study results to patients and the wider public. Patients and carers will also be made aware of the findings through patient associations and special interest/focus groups. Lay summaries written in conjunction with the patient advisory group and the patient representative on the TSC in conjunction with scientific abstracts and publications will be published on the study website. Video presentations and podcasts will be uploaded on the University website so that interested parties may access the work in bite-sized quantities.

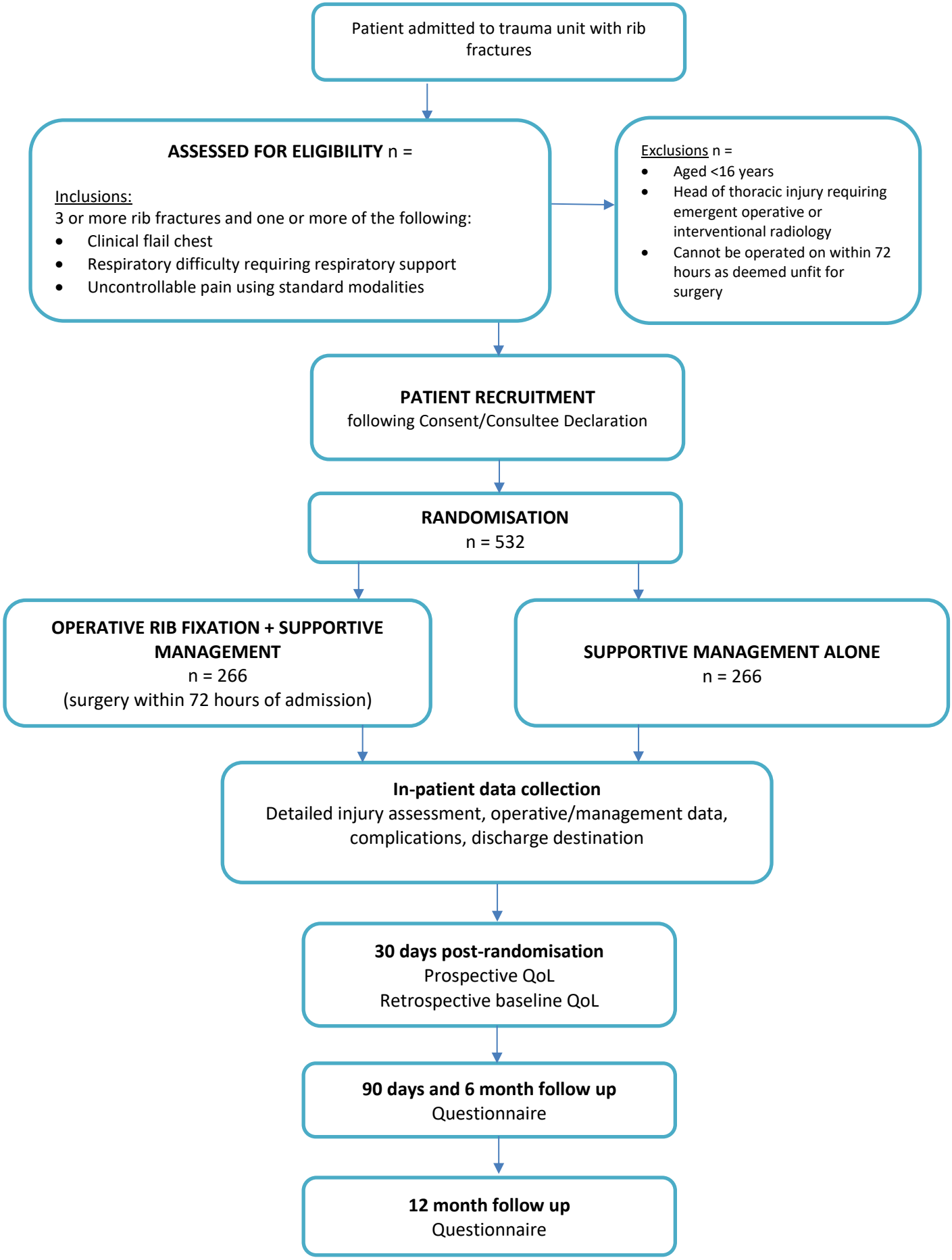
16. PUBLICATION POLICY

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the ORiF Trial Management Group, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the ORiF collaborators. To safeguard the integrity of the

main trial, reports of satellite studies will not be submitted for publication without prior agreement from the ORiF Trial Management Group.

Authors named in the publication will be agreed by the Trial Management Group. These may include, but are not limited to: co-applicants on the funded grant, members of the Trial Management Group, and Principal Investigators who have demonstrated a commitment to and throughout the trial. Contributors will also be agreed by the Trial Management Group and acknowledged accordingly in any publication.

17. APPENDIX A: STUDY FLOW CHART



18. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	Assessments							
	Recruitment	Treatment	Discharge	30 days	6-8 weeks	90 days	6 months	12 months
Informed consent/consultee agreement	X							
Patient demographics	X							
Detailed Injury assessment (medical history, physical examination)	X							
Eligibility assessment (Including CT scan)	X							
Randomisation	X							
Operative details (if applicable)		X						
In-patient management details from TARN & CRFs (ventilator days, length of stay. complications, discharge destination)			X					
X-rays (operative group only)					X			
Mortality data								X
Quality of Life questionnaires (EQ-5D-5L/3L)				X (additional retrospective baseline for EQ-5D-5L/3L)		X	X	X
Function-related questionnaire and pain VAS						X	X	X
Health Resource Use							X	X

19. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	11Jan2019	Associate Professor Benjamin Ollivere	• Removal of AIS 3+ as an inclusion requirement/minimisation factor. • Consistency in inclusion criteria wording to patients with '3 *or more* rib fractures', rather than '3+ rib fractures.' • Clarification on the pre and post-intervention dual consent process, in particular the consultee declaration process. • Other minor administrative changes.

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