The Operative Rib Fixation Study

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.

Statistical Analysis Plan

Version 1.0– 20Dec2024

Based on Protocol version 6.0 – 10Jul2023

Trial registration: 10777575

Oxford Clinical Trials Research Unit (OCTRU)
Centre for Statistics in Medicine (CSM)

CONTENTS

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme funded 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. This Statistical Analysis Plan (SAP) cover the planned statistical analyses only and not the trial health economic analyses. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Key personnel

Author (Trial statistician):

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Professor Jonathan Cook (Senior Statistician)

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1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_20Dec2024		Protocol_V6.0_10Jul2023	Not applicable as this is the 1st issue

2. BACKGROUND AND OBJECTIVES

2.1 Background and rationale

Chest injuries are one of the commonest causes of death following trauma and 16% of patients suffering major injuries have rib fractures (1). 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 (2). 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 (1).

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 (3). TARN data also shows patients recover quicker and have better health outcomes with rib fracture fixation plus supportive management (3). The addition of surgery for these patients increased in frequency by 320% between 2014 and 2015 (1). This is despite the lack of rigorous evidence, or a health economic analysis to prove its efficacy.

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 (8). 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.

2.2 Objectives

The purpose of this randomised controlled trial is to compare supportive management alone with supportive management with the addition of operative rib fixation in patients with multiple rib fractures, which will be measured in terms of both patient mortality and quality of life. The research hypothesis is that patient mortality levels will be lower, and quality of life will be better in patients who undergo both supportive management and operative rib fixation when compared with those receiving supportive management alone.

The study will assess the clinical management pathways for these patients within the first 72 hours of their injury, upon inpatient admission to the hospital.

The primary objective for this study is patient mortality, with quality of life a key secondary focus. All data will be collected over a period of 12 months.

	Objectives	Outcome Measures
Primary Outcome	To assess differences in all-cause mortality between the intervention and control groups over 12 months.	All-cause mortality data
Secondary Outcomes	• To assess and draw inferences from observed differences between the intervention and control groups in quality of life at 12 months following injury. • 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 clinical management process outcomes e.g., length of stay (LOS) and ventilator days 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.	• EQ-5D-5L index with direct trial collection of primary outcome data • 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) • Health Resource Use questionnaire • TARN data for both randomised and non-randomised patients

3. STUDY METHODS

3.1 Trial Design/framework

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 a minimum of 15 Major trauma centres/units across the UK. The trial will compare the initial management for patients with severe chest wall injury. Patients will be randomised to receive either non-invasive supportive management or supportive management with the addition of operative rib fixation. More detailed definitions of the interventions can be found in the study protocol ORiF_Protocol_V6.0_10Jul2023. A clinical and cost effectiveness evaluation will be undertaken up to 12 months following treatment, with data

collection at 30 days, 3, 6 and 12 months. Primary data collection will be collected both by the local study team, with supplementary collection of data through the TARN network as part of standard of care.

3.2 Randomisation and Blinding

Randomisation will be performed using a web based automated computer generated 1:1 minimisation with treatment groups balanced for: age (<65 years or ≥65 years), gender, polytrauma, mechanical ventilation and study centre. The minimisation algorithm will incorporate a probabilistic element which has been set to 0.8. This ensures that there is an 80% probability that the participant will follow the minimisation algorithm, with a 20% probability of being allocated via simple randomisation. This ensures that there is a 90% chance a participant receives the treatment which minimises characteristic imbalance.

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 as a target 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 logins to the web-based system.

Full details of the randomisation are available in ORiF_RBP_v2.0_04Mar2019_signed.pdf, stored in the confidential statistical section of the TMF.

Neither participants nor operating surgeons can be blinded to receipt of the surgery.

3.3 Sample Size

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.(4-7) 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 are also sufficient for the EQ-5D-5L, based upon a target mean difference of 0.09 (an important difference for EQ-5D-3L) (14), 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).

The study protocol was amended on 21Oct2022 to change EQ-5D-5L from a co-primary outcome to a secondary outcome.

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

A Data and Safety Monitoring Committee will oversee the conduct of the trial and safety of participants by reviewing accruing blinded data during recruitment and follow-up including any planned interim analyses. The full remit is stored in the DSMC Charter ORiF_DSMCCharter_V1.0_17Dec2018 as per OCTRU SOP GEN-011 Trial Committees.

3.5 Timing of Final Analysis

A single set of final analyses will be performed at the end of the follow-up.

3.6 Blinded analysis

The statistician will not be blinded to the intervention allocation. Results will not be viewed by clinical investigators and other non-statistical trial team members until this SAP has been agreed, follow-up data is complete, and data cleaning has been undertaken.

3.7 Statistical Analysis Outline

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 outcomes. Analyses will be carried out in Stata software version using the newest version available at the time of analysis (currently 18.0) or R.

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

Statistical significance will be at the 2 sided 5% level with corresponding 95% confidence intervals derived. Only a single main analysis is planned once the study data collection is complete. No formal stopping rules are accounted for in the sample size and accordingly no formal interim analyses are planned. Correspondingly, no adjustment for multiplicity will be undertaken. In the statistical analyses, one primary outcome of mortality is viewed as clinically important in its own right and will be evaluated independently.

4.2 Definition of Analysis Populations

The principal analysis will be performed on the as randomised (AR) population, whereby all participants included in their randomised groups will be analysed, to which they were originally allocated irrespective of compliance to the allocation.

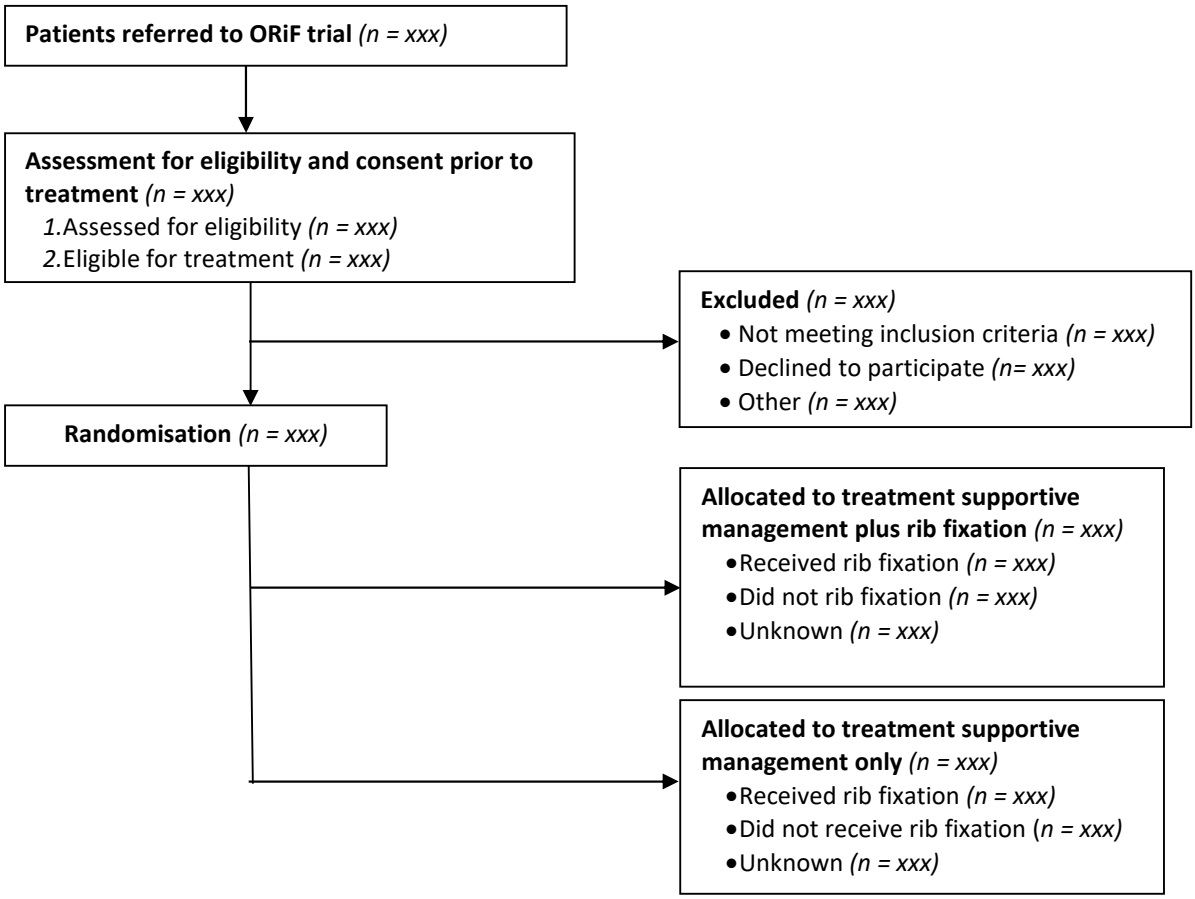
Per protocol (PP): The AR population with some excluded participants, where exclusions should be detailed and could include protocol violations/deviations, participants who did not receive the intervention or did not receive the allocated intervention as planned, participants with extensive missing data. Details of participants to be excluded from the final analysis will be finalised prior to the final analysis beginning.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome is provided following the appropriate guideline (e.g. CONSORT). Protocol violations/deviations and information relating to the screening data including the number of ineligible patients randomised, together with reasons. Information on number of participants screened, found to be ineligible (with reasons where available), refused to participate (with reasons where available) should also be included. The CONSORT flowchart (Figure 1) provides an overview.

Figure 1: Flow diagram of the ORiF trial – recruitment and randomisation.



5.2 Withdrawal from treatment and/or follow-up

The numbers (and percentages) of withdrawals/loss to follow-up together with reasons will be reported by rib fixation plus supportive management and supportive management alone separately. Any deaths (and their causes) will be reported separately.

5.3 Baseline Characteristics

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

5.4 Unblinding

Participants and operating surgeons are unblinded to receipt of the surgery, as are site staff.

5.5 Treatment Compliance with Details of Intervention

The compliance with randomised treatments will be reported by supportive management plus rib fixation and supportive management. Compliance in the supportive management plus rib fixation group will be defined as receiving rib fixation within 72 hours. Compliance in the supportive management only group will be defined as the avoidance of rib fixation at least within the first 72 hours and subsequently only undertaken if clinical status of participant has changed. 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. These circumstances include but are not limited to: Deterioration in physiological status making the patient unsuitable for surgery; Requirement for urgent intervention (other than those listed in the exclusion criteria) rendering the patient unsuitable for fixation; Development of acute sepsis prior to surgery making metalwork implantation inappropriate. Compliance to allocation will be collected using a separate bespoke CRF to supplement the data recorded within TARN. Participants wanting to withdraw from the follow up will be asked to consider allowing the continuation of the collection of their related TARN data (England and Wales only).

5.6 Reliability

Sites will take the responsibility to double check the mortality and death information collected from ORiF_DeathNotificationForm_V1.0 for all randomised patients via NHS Spine or other hospital records. Mortality information beyond 12 months will be sought where possible for participants until the end of study follow-up using these same sources.

6. ANALYSIS

6.1 Outcome Definitions

6.1.1 Primary outcome

The primary outcome is all-cause mortality data over 12 months:

Differences in all-cause mortality between the control (supportive management alone) and the intervention (supportive management + operative rib fixation) over 12 months will be assessed. This data will be collected from trial sites directly on a monthly basis. Sites are also directed to complete a death notification CRF and return to the trial management team when they become aware of a patient's death.

All-cause mortality will be analysed as a time-to-event outcome which is overall survival (time from randomisation to death). Date and cause of death will be collected from the death notification form.

Overall survival is defined as the time from randomisation to death; participants who survive until the end of the trial follow-up, withdraw from the trial and lost to follow-up will be censored at that point.

6.1.2 Secondary Outcomes

Quality of life: The EQ-5D-5L is defined as a self-assessed, health related, quality of life questionnaire. The scale measures quality of life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Data on participants' quality of life will be collected at baseline (collected retrospectively before discharge), 30 days, 3 months, 6 months, and 12 months post-randomisation. The outcome for quality of life will be collected via the EQ-5D-5L questionnaire in the patient questionnaire booklets at these time points. These questionnaires are patient reported, requiring patients to complete and return them to the trial team independently, either by post or electronically. The EQ-5D-5L has two components – the descriptive system and the visual analogue scale (VAS). The descriptive system consists of five domains of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) scored on a five-level response (no problems, some problems, moderate problems, severe problems, and unable). The VAS measures health from 0 (worst imaginable health state) to 100 (best imaginable health state).

Patient reported pain: Participants will be asked to complete the Visual Analogue Scale (VAS) measuring the amount of pain they are in due to their ribs at 3 months, 6 months, and 12 months post-randomisation in the patient questionnaire booklets. The VAS scale is a line with 0 at one extremity (no pain) and 10 at the other (worst possible pain).

Length of hospital stay (primary visit): Length of hospital stay is defined as the period time of from patient's admission to ward. Length of hospital stay will be compared between the intervention arms. Date of discharge will be collected from a discharge form completed upon the patient being discharged from hospital. Length of stay will be obtained by calculating the difference between the date of randomisation and the date of discharge. Length of stay will also be collected in the TARN database; this data will be checked against the CRF calculation.

Ventilator days: The ventilator days is generally defined as the number of days the patients was using mechanical ventilation in hospital. It will be assessed by intervention and control arm. The ventilator days will also be collected in the TARN database; the data will be checked against the CRF calculation.

Further intervention: The two intervention arms will be compared on the incidence of further intervention beyond the randomised treatment. This data will be obtained from the TARN database.

Cost-effectiveness at 6 months and 12 months: Cost-effectiveness outcomes will be obtained via a Health Resource use questionnaire. The cost-effectiveness analysis will be undertaken by the trial health economist.

Generalisability of the findings: 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 and will be compared between randomised and non-randomised patients who exist in TARN database but not in ORiF trial. In addition, any requirement for respiratory support will be collected. All this information will also be recorded in TARN database. A recent statistical approach assesses the generalisability of the findings from the randomised trial against the population registry data.

6.2 Analysis Methods

6.2.1 Primary Outcome Analysis

The primary outcome for this study is all-cause mortality (time-to-death) over 12 months.

The analysis of the primary outcome will be a time-to-event analysis using a Cox proportional hazard regression model with allocated group (rib fixation/supportive management only) as a predictor and minimisation factors (age, gender, centre, polytrauma and mechanical ventilation) as covariates. The specific estimate of interest is the coefficient for the allocated group taken from the model. An unadjusted analysis on all-cause mortality will also be carried out with log-rank (simple and stratified for clinical minimisation factors except for site) tests. All available mortality data will be used including follow-up beyond 12 months in order to estimate early mortality more precisely (up to 12 months).

The assumption of proportional hazard for the Cox model will be examined. One of the assumptions is the model is linear with the help of martingale residual plot and the other one is the hazard function keeps constant over time by using Schoenfeld residual plot. If the proportional hazard assumption is not met, parametric survival analysis or restricted mean survival time, such as the accelerated failure time method will be considered. However, initially adjustments to the Cox model (interaction effect), and the use of stratified Cox regression will be explored. A Cox model may still be used for the main analysis if the interpretation as a weighted average over the time period is considered tenable and useful. Overall survival will be presented as Kaplan-Meier plot by treatment groups. Kaplan-Meier plots will present numbers at risk, and events at the end of each time interval (30 days, 3 months, 6 months, 12 months and beyond) will be summarised. Median overall survival will be reported.

The primary outcome analysis will be analysed on as randomised (AR) population. A further secondary analysis will be on the PP population. Participants who withdrew will be censored at the last date overall survival data was available.

All principal analyses will be performed at the 2-sided 5% significance level.

6.2.2 Secondary Outcome Analysis

Secondary analyses will explore the influence of differential outcomes on treatment effect by assessing generalised linear multilevel models with adjustment for minimisation factors (age, gender, polytrauma, mechanical ventilation and study centre) and baseline variables as appropriate. If adjusted for minimisation leads to convergence, or validity issues a simplified analysis excluding study centre and/or all adjustments will be undertaken.

All secondary analyses will be analysed on as randomised population performed at the 2-sided 5% significance level. A further secondary analysis for EQ-5D-5L index score will be on the per protocol population.

Quality of life

EQ-5D-5L is a standardised instrument for measuring health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and visual analogue scale (VAS). EQ-5D index score indicating the patient's overall health status is derived from a set of five questions (EQ-5D-5L or EQ-5D-3L) and EQ-VAS score can be utilised a measure of health outcome that reflects the patient's own judgement.

The EQ-5D questionnaire has been shown to be responsive, including when reported by proxy among those with cognitive impairment. Index scores from the EQ-5D-5L descriptive system will be generated using a

mapping function converting the 5L responses to a 3L index score. The Van Hout et al. 2012 (17) mapping will be used in the main analysis of EQ-5D and a sensitivity analysis will another mapping function e.g. Hernandez-Alava et al. 2018 as implemented in Stata command. 0 values will be used to represent death. The impact of this imputation for death will be assessed in a sensitivity analysis. An unadjusted analysis on EQ-5D-5L will be performed using a t-test.
Individual EQ-5D-5L and EQ-5D-3L responses will be presented descriptively. EQ-5D-5L and EQ-VAS will both be analysed using linear regression models. Treatment groups will be compared adjusting for at baseline score (pre-injury), age, gender, polytrauma, mechanical ventilation and study centre as fixed effects. Adjusted mean differences and associated 95% confidence intervals and p-values will be reported. If there are convergence issues the model will be simplified by removing study centre, and/or all minimisation variables. The EQ-5D-3L index score will be analysed by using the same model as the EQ-5D-5L index score.

Patient reported pain, length of stay and ventilator days
These outcomes will be summarised by treatment group using numbers and percentages. To estimate the treatment effect, mixed linear models adjusting for age, gender, polytrauma, mechanical ventilation as fixed effect and with a random effect for study centre. Adjusted mean differences will be presented with associated 95% confidence intervals and p-values. Sensitivity to any potential differential mortality treatment effect will be considered, and if appropriate further analyses conducted.

Health Economic Analysis
This document does not cover the health economic analyses which will be addressed elsewhere.

Generalisability of the findings
TARN data for both randomised in ORiF and non-randomised patients who are recorded in TARN database but did not participate in study trial will be used for assessing the generalisability. Assessment of the *a posteriori* (also called sample-driven) generalisability is planned. Demographics such as age and gender, length of stay, injury severity score and survival rate will be compared between two group of patients. (15-16) More formal, complex ways to assess the generalisability will be part of the OPERA (The ORiF Procedure Mechanisms of Rib Fixation) sub-study, and details of the corresponding analyses are beyond the scope of this SAP.

6.3 Missing Data

The impact of missing data will also be explored in sensitivity analyses using appropriate methods for the key secondary outcome, EQ-5D-5L utility (11) (e.g. the rctmiss Stata command for assessing the impact of missing not at random for EQ-5D-5L utility using a pattern mixed-model based approach) (12).

6.4 Sensitivity Analysis

Sensitivity analysis on the primary outcome will explore the presence of informative censoring. Sensitivity analyses will be used if proportional hazards assumption appears to be untenable, and/or adjustment for minimisation variables is problematic. Use of a parametric survival model will require sensitivity analyses to explore the impact of related assumptions. Complier average causal effect (CACE) type approach will be used to assess sensitivity to compliance regarding receiving rib fixation (13). A further analysis of the primary outcome will consider potential impact of COVID-19 pandemic if sufficient mortality events in the relevant time periods (pre/post/after) are available.

6.5 Pre-specified Subgroup Analysis

Exploratory subgroup analyses for the primary outcome will explore the possible treatment effect modification of clinically important minimisation factors (age, gender, polytrauma and mechanical ventilation), using treatment by factor interaction and will be interpreted cautiously.

Another subgroup analyse will be focus on the treatment effect modification of injury severity ISS (injury severity score) and AIS (Abbreviated Injury Scale).

The possibility of treatment effect modification of ventilator-free days by mechanical ventilation status at baseline will be explored by extending the linear mixed model with adjusting for the randomisation and including a treatment-by-subgroup interaction effect.

They will be analysed at the 2-sided 5% significance level but will be interpreted cautiously and considered and labelled as exploratory accordingly.

6.6 Supplementary/ Additional Analyses and Outcomes

Complier average causal effect (CACE) type approaches will be used to analyse primary outcome (all mortality data) with reference to the impact of non-compliance (13).

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 (10).

For TARN analysis, patients will be included when a patient's TARN ID is complete and not missing.

Starting from the 2nd April 2024 TARN will operate under the NHS England Patient Outcomes and Registry Programme (ORP) as the National Major Trauma Registry (NMTR).

TARN data accuracy will be explored by comparing to the trial data where available for both. Mortality, length of stay in hospital and EQ-5D-5L index score will be compared between the ORiF trial bespoke data and the routinely collected TARN data. Age and gender distributions will be compared graphically between two treatment groups to explore differences in clinical populations.

The TARN population overall and by reference to the subset most relevant to ORiF will be summarised as appropriate given the available data. The main prognostic variables of interest in the TARN dataset are injury severity score and probability of survival. The number and percentage of age with four categories, <16, 16-35, 35-65, 65-80 and >80, gender, mechanism of injury, mechanism type, transferring out reason, most severely injured body region, injury severity score band with two categories, >15 and <=15 will be compared between two the treatment groups.

Number, median and range of length of hospital stay, length of stay in critical care, and number, median and interquartile range of all caused of mortality within 30 days, probability of survival and ISS will be compared to two treatment groups though without formal comparison.

Additional assessments of generalisability will be conducted both informally in terms of population characteristics and also consistency of estimates using propensity score weighted analysis are planned related to the ORiF OPERA sub-study. The scope of these is beyond this SAP and will be confirmed prior to start the OPERA sub-study analysis.

6.7 Harms

The evaluation of harms is integral to the study and in terms of the aims of the study are covered by the primary and secondary outcomes. Regulatory safety events (i.e. serious adverse events) will be summarised according to the approach summarised in the trial protocol.

6.8 Health Economics and Cost Effectiveness

Details of the Health economic analysis is beyond the scope of the document and are anticipated to be outlined in a separate Health Economic Analysis Plan.

6.9 Meta-analyses

No meta-analysis of the findings of ORiF with other studies are planned as part of the main trial analysis.

7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome and key secondary outcomes (all mortality data and EQ-5D-5L index and VAS score at retrospective baseline, 30 days, 3 months, 6 months, 12 months) a statistician not involved in the trial will independently repeat the analyses detailed in this SAP, by using different statistical software (if possible). The results will be compared and any discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report). Both all mortality data and EQ-5D-5L require derivation to analyse. These derivations will need to be performed by the second statistician to ensure they have been performed correctly, and well as a check of the analysis model and reporting of results.

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS or R. The relevant package and version number will be recorded in the Statistical report.

9. PUBLICATION

This study has been conducted as part of the portfolio of trials in the registered UKCRC Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. It has followed their Standard Operating Procedures ensuring compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and any applicable regulatory requirements.

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11. APPENDIX: GLOSSARY OF ABBREVIATIONS

SAP	Statistical Analysis Plan
DSMC	Data and Safety Monitoring Committee
TSC	Trial Steering Committee
CI	Chief Investigator