PRESTO

Pragmatic Randomised Evaluation of Stable Thoracolumbar fractures: a feasibility study

STATISTICAL ANALYSIS PLAN

v. 1.1

York Trials Unit
Department of Health Sciences
University of York
York, YO10 5DD

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Author(s): Elizabeth Coleman & Jenny Roche
Chief Investigator: Arun Ranganathan
Trial Coordinator: Liz Cook

Contents

This analysis plan deals only with the statistical analysis of efficacy, any cost-effectiveness analysis will be detailed in a separate plan.

1. Definition of terms/acronyms

CRF	Case Report Form
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Score
PROM	Patient reported outcome measure
ODI	Oswestry Disability Index
RCT	Randomised Controlled Trial
SF-12	Short Form-12
SOP	Standard Operating Procedures
VAS	Visual Analogue Scale
YTU	York Trials Unit

2. Trial Objectives

PRESTO is a feasibility study aimed at establishing whether it would be possible to deliver a full-scale randomised controlled trial (RCT) comparing surgical fixation to non-operative management for patients with a stable thoracolumbar fracture, without spinal cord injury.

To establish this, several aspects will need to be considered, both qualitatively and quantitatively:

1. Are surgeons willing to randomise eligible patients and adhere to randomisation?
2. Are patients willing to be randomised and adhere to randomisation?
3. What is the completeness of follow-up in this population?
4. Are there a sufficient number of centres and surgeons willing to participate in a future RCT, to make the trial feasible within a viable timescale?
5. What methods of establishing spinal stability and suitability for surgery or non-operative management are currently used?
6. What methods of surgical fixation and non-operative management are currently used?
7. What are the barriers to successful delivery of the future trial and how can they be overcome?
8. Can the British Spine Registry be used to collect participant data in a trial?
9. What is the most suitable primary endpoint for a main trial?
10. How can we accurately identify, quantify and value economic data to capture the impact of the two treatments on the NHS and productivity?

3. Design

PRESTO is an open, pragmatic, parallel group randomised external feasibility trial. At three sites in the UK, Leeds, Cardiff and London, participants with a stable thoracolumbar fracture will be randomised to either surgical fixation, or non-operative management.

Full details of the background and design of the trial are presented in the protocol (version 1.1). The protocol (version 1.1) states that the statistician will be blinded for the analysis however this will no longer viable as the trial processes that are in place are not conducive for the statistician to remain blind. This is something that could be addressed in the planning of a future trial.

4. Sample Size

Based on initial discussions with the centres it is estimated that there will be at least 120 eligible patients. We aim to recruit 50% of eligible patients giving a sample size of 60. If we identify 120 eligible patients, as anticipated, we will be able to estimate a participation rate of 50% to within a 95% confidence interval of ±9%. The size of this trial is in line with guidance on the size of feasibility trials, which suggests there should be at least 12 participants in each arm at the analysis stage (Julious, 2005).

5. Randomisation

Participants will be randomised to either surgical fixation or non-operative management on a 1:1 basis, using block randomisation, with blocks of varying lengths, stratified by centre and type of injury (high/low energy). This will be undertaken using a secure, internet-based randomisation service hosted by York Trials Unit (YTU), ensuring allocation concealment and immediate unbiased allocation. However, both the participant and their treating surgeon will be informed of this allocation and therefore will not be blinded to allocation. In addition, it will not be possible to blind outcome assessors in this trial.

6. Outcomes

6.1 Primary outcome

For this feasibility trial the primary outcome is recruitment rate, defined as the proportion of eligible participants who are randomised throughout the study. This will allow for calculations to be made to determine if it would be feasible to undertake a large scale RCT in this area.

6.2 Secondary outcomes

There will be a range of secondary outcomes, which can be categorised into the following areas: randomisation, drop-out, cross-over, loss to follow-up, completeness of outcome data, study processes and details of the interventions delivered. To quantify these, the following aspects will be reported.

Recruitment:

- Number of eligible patients;
- Proportion of eligible patients approached for consent;
- Proportion of eligible patients not approached for consent, and reasons why;
- Proportion of patients who provided consent;
- Proportion of patients who did not provide consent, and reasons why.

Randomisation:

- Proportion of patients providing consent who are randomised;
- Proportion of patients randomised who do not receive the randomly allocated treatment and reasons why.

Cross-over:

- Proportion of patients randomised to the non-operative treatment who receive surgical management, at what time point and reasons why.

Drop-out:

- Proportion of patients dropping out between randomisation and follow-up at each time-point and reasons why.

Ability to collect clinical outcome measures:

- Feasibility of gathering patient reported outcome measures and other outcome measures at baseline and follow-up (proportion of complete data for each outcome measure; proportion successfully gathered through the British Spine Registry).
- Feasibility of gathering data on complications and adverse events (proportion of complete data).

To inform the design of the future trial we will also gather data on:

- Participant treatment preferences at baseline;
- Clinical care during the trial:
  - Methods used to establish spinal stability.
  - Details of surgical fixation used
  - Details of non-operative management.

6.3 Follow-up

Follow-up of participants will take place at 2 weeks and 3 month post randomisation. In addition, a 6 month follow up will be completed for all participants who were randomised in the first nine months of recruitment, as they will reach this point within the follow-up period. This is expected to be around two-thirds of the participants, approximately 40.

In addition, the following information will be collected at all follow-up time points:

- Treatment information
- Rehabilitation information (type and number of appointments)

6.4 Other important information

As well as those listed above, the following information will also be collected and reported:

- Length of hospital stay;
- Time to return to work and details about return (whether individuals return to their previous job, a less physically demanding role, and whether there are any job modifications such as returning on reduced hours), and
- Return to normal activities (e.g. volunteering, sports, and hobbies).
- Kyphotic Angle Measurement (baseline and follow-up)
- Patient and surgeon preference (at baseline)

Baseline characteristics of the randomised participants will also be collected, including age, gender and ethnicity, as well as any complications and AEs encountered within the trial. Basic health economic data will also be collected and reported in the health economic analysis.

6.5 Outcome Measures

The following outcome measures will be collected at baseline, 3 and 6 month follow-up. They will be derived as indicated below. At baseline, some outcomes will be measured twice, in order to collect data about the patient pre-injury and post-injury. Throughout this SAP, the term baseline will represent a measurement taken post-injury, unless specified otherwise.

ODI

The ODI is a commonly recommended patient reported outcome measure (PROM) for low back pain and spinal surgery (Clement et al., 2015; Davidson and Keating, 2002; Deyo et al., 1998). It assesses limiations acrosss ten aspects of daily living, each scored 0 to 5 (Fairbank and Pynsent, 2000). The ODI will be collected pre-injury (collected at baseline), at baseline, month 3 and month 6.

A score can be calculated for the ODI if 9 or 10 of the 10 questions have been completed, that is if at most one question is unanswered. This can be scored in the following way:

$$\frac{Total\ score}{Total\ possible\ score\ (= 50\ or\ 45)} * 100$$

The total possible score will be 50 if all questions have been answered, and 45 is one was missing. The total score is the summation of all of the responses given, and will be between 0 to 50. These percentages can be categorised in the following way, where a higher score indicates a higher level of disability.

0% - 20%	Minimal disability	The patient can cope with most living activities. Usually no treatment is indicated apart from advice on lifting sitting and exercise.
21% - 40%	Moderate disability	The patient experiences more pain and difficulty with sitting, lifting and standing. Travel and social life are more difficult and they may be disabled from work. Personal care, sexual activity and sleeping are not grossly affected and the patient can usually be managed by conservative means.
41% - 60%	Severe disability	Pain remains the main problem in this group but activities of daily living are affected. These patients require a detailed investigation.
61% - 80%	Crippled	Back pain impinges on all aspects of the patient's life. Positive intervention is required
81% - 100%	Bed Bound	These patients are either bed-bound or exaggerating their symptoms.

VAS

The VAS is a unidimensional measure of pain intensity which has been widely used in diverse adult populations (Hawker et al., 2011; McCormack et al., 1988). The VAS will be collected at baseline, month 3 and month 6.

This is a continuous 11-point scale, anchored by two verbal descriptors with 0 representing ‘no pain’ and 10 representing ‘worst imaginable pain’, to measure average pain. Participants mark on the scale where they would describe their pain to be.

SF-12

The SF-12 consists of 12 items, and is a widely used measure of physical and mental health completed by the participant, the population norms of which have a mean of 50 and standard deviation of 10; higher scores indicating better health (Ware et al., 1996). The rationale for including the SF-12 is that it is feasible that a delay to return to work and recreational activities could impact on participants’ ability to perform other daily activities and their

emotional well-being. The SF-12 will be collected pre-injury (collected at baseline), at month 3 (via post questionnaire only) and month 6 (via postal questionnaire only).

The SF-12 consists of eight health domain scales that are comprised of either 1 or 2 questions. If a response is missing for a single question in a health domain that consists of two questions, it will be replaced by the value of the other response in that domain (and hence will no longer be considered missing). If a response is missing for a single-item domain this will remain missing. The physical and mental component scores (PCS and MCS) can only be calculated if there are values for all 12 items.

EQ-5D-5L

The EQ-5D-5L is a validated generic patient-reported outcome measure (EuroQol,2017). The descriptive system has five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with five response options for each domain (no problems, slight problems, moderate problems, severe problems and extreme problems). In addition, it has a health status visual analogue scale (VAS) which measures self-rated health with endpoints ranging from 'the best health you can imagine' to 'the worst health you can imagine'. The EQ-5D-5L will be collected pre-injury (collected at baseline), at baseline, month 3 and month 6, and will be evaluated in the health economic section of the report.

7. Data

7.1 SOPS

Data and documents relevant to the statistician will be kept in a Statistical Master File following the directory structure detailed in the YTU SOP entitled "Directory structure and version control" (SOP ID: DS01, version 3.0, 4 May 2016).

7.2 CRFs

A copy of the CRFs with the variable names from the database (known as 'specs') will be kept by the Trial Statistician in their Trial Statistics folder.

7.3 Management of datasets and data verification

All data collected by sites using paper CRFs will be mailed to YTU, where it will be scanned into a secure web-based interface. Routinely collected data may be received electronically, and these will be merged with the other data by the trial statistician.

All data will be stored and transferred following YTU SOPs. Data will be checked according to procedures detailed in the trial specific Data Management Plan, following validation plans authorised by the trial manager, and trial statistician.

All data recorded electronically at YTU will be held in a secure environment at the University of York. Full data backups are performed nightly, using rotational tapes, to provide five years' worth of recoverable data.

7.4 External datasets

As part of the feasibility aspect of this trial, the British Spine Registry will be used to collect patient reported data, to assess the viability of this method for a future trial. Hospitals are required to upload patient data via a third party platform onto the British Spine Registry for

any spine injury already. In this instance a modified version of the entry platform has been set up for the use by the PRESTO team, to allow all patient reported outcome measures required by the trial protocol to be collected via this system at three and six months. Participants will have the option to receive email alerts to fill in the questionnaires via the British Spine Registry portal, or to have postal questionnaires. If the online version is chosen, and the participant does not complete the questionnaire within 3 weeks, a paper version will be posted out to them. Any outcome data collected via the British Spine Registry will be downloaded from the portal once follow-up has finished, and combined with the data held by the YTU team. The viability of using this method will be measured by the proportion and completeness of the data.

8. Analysis

A CONSORT diagram (Consolidated Standards of Reporting Trials, 2010) will detail the flow of participants through the trial, see Appendix. A single, descriptive analysis will be performed at the end of the trial, using Stata v15 or later (Stata Corp.) No formal analysis will be undertaken in this trial, as it is a feasibility trial.All analyses will be undertaken unblind by the trial statistician.

8.1 Baseline data

All participant baseline data will be summarised descriptively by trial arm as randomised. No formal statistical comparisons between groups will be undertaken. Continuous measures will be reported as means, standard deviations, medians, minimums and maximums, while categorical data will be reported as counts and percentages. Number of missing responses will also be reported where applicable.

8.2 Primary analysis

The primary analysis will be the representation of the recruitment rate. This is defined as the proportion of eligible patients who were randomised into the trial. A 95% confidence interval will be presented along with this proportion. This will allow for future calculations to be undertaken, to determine how many sites and the length of the recruitment period that would be needed for a future trial. The recruitment rate will also be displayed graphically showing monthly, and overall recruitment by hospital site.

8.3 Secondary analyses

All proportions listed as secondary outcomes in Section 6.2 will be reported in a similar way to the primary analysis.

The viability of using the British Spine Registry will be assessed by considering the proportion of data successfully gathered through it. A summary of data which are consistently collected and poorly collected using the Registry will be detailed. In addition, the number of participants who agreed to provide data electronically and then who later in fact returned paper CRFs will be detailed.

More generally, if a patient does not return follow-up forms, they may be contacted by phone. It will be reported how often data is collected in this manner.

Details on patient and surgeon treatment preference at baseline will be detailed by counts and percentages for each option, as well as the number of missing responses.

Information on rehabilitation (type and number of appointments) will be described by trial arm. Length of hospital stay, time to return to work, kyphotic angle measurements and time to return to normal activities will be summarised descriptively for each arm, in weeks, and the amount of missing data summarised.

ODI scores will be described descriptively overall and by treatment arm with the mean, standard deviation, minimum, median and maximum score reported. The numbers of patients in each disability category will also be described descriptively overall and by treatment arm. The number of missing responses will be summarised and it will be noted if a score could not be calculated due to missing components.

Scores from the VAS will be described descriptively overall and by treatment arm with the mean, standard deviation, minimum, median and maximum score reported. The number of missing responses will be noted.

Scores on the SF-12 will be used to calculate physical component scores (PCS-12) and mental component scores (MCS-12). They will be described descriptively overall and by treatment arm with the mean, standard deviation, minimum, median and maximum score reported, at baseline, month 3 and month 6. The number of missing responses will be summarised and it will be noted if a score could not be calculated due to missing components.

Mean scores, broken down by treatment group, for the ODI, VAS and SF-12 will also be summarised using line graphs.

8.4 Adverse events

In this trial, both complications and adverse events will be reported, as well as details on any additional surgery. Due to one arm of the trial being surgery, there are a number of complications that would be expected, and as such will not be deemed an adverse event in this instance. Expected complications include, but not limited to, death within 30 days of surgery, neurological complications, deep wound infections and skin problem. Further details can be found in the trial protocol.

All complications, and adverse events will be described by trial arm. Details will include number of events, type of event, seriousness and expectedness. Analyses will be purely descriptive.

8.5 Planned interim review and analyses

The combined TSC DMEC will meet at least once a year, but more often as required. Simple summary statistics will be produced for these meetings, including reporting baseline characteristics. No interim analyses will be undertaken, and no formal stopping rules are envisaged within this trial.

9. SAP amendment log

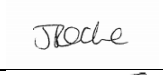
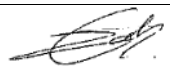
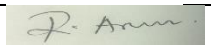
All changes that are made to the Statistical Analysis Plan following initial sign-off will be noted in the box below. This will include details of the changes made, any notes/justification

for these changes, the new version number if applicable, who the changes were made by, and the date.

Amendment/addition to SAP and reason for change	New version number, name and date
Changes to Section 6.5, related to the scoring of the SF-12. The original scoring method was for the SF-12v1 instead of the SF-12v2, hence an amendment was necessary to include the correct scoring information for v2.	*V1.1, J.Roche, 05/07/2019*

10. Signatures of approval

Sign-off of the final approved version of the Statistical Analysis Plan by the Chief Investigator, Trial Co-ordinator and Trial Statistician

Name	**Trial Role**	**Signature**	**Date**
Jenny Roche	Statistician		09/08/19
Liz Cook	Trial-Coordinator		09/08/19
Mr Arun Ranganathan	CI		09/08/19

11. References

PRESTO PROTOCOL

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12. Appendices

Below are some examples of tables and figures that may be used to report the results of PRESTO; however these may differ to those that are used.

Table One: Baseline characteristics for randomised participants

	Surgery Arm (n=)	Non-operative Arm (n=)	Overall (n=)
Age (years) Mean (SD) Median (min, max)			
Ethnicity, n(%) White Black Asian Chinese Other Missing			
Qualifications, n(%) No formal qualifications Some qualifications Degree or higher Missing			
Employment, n(%) Part-time Full-time Self-employed Student Retired Looking after family or home Not employed – seeking work Other Missing			
Smoker, n(%) Yes No Missing **If yes:** **Number of cigarettes per day**			

Mean (SD) Median (min, max) **Number of years a smoker** Mean (SD) Median (min, max) **If no:** **Have you smoked in the past?** Yes No Missing **If yes:** **Number of years a smoker** Mean (SD) Median (min, max) **Number of years since stopping** Mean (SD) Median (min, max)			
Alcohol, n(%) Yes No Missing **If yes, how many units per week?** 0 – 7 8 – 14 15 – 21 21 + Missing			
Diabetic, n(%) Yes No Missing			
Steroids, n(%) Yes No Missing			
Living Arrangements, n(%) Alone Alone but with support With partner With friends With relatives			

Care home Other Missing			
Occurrence of injury, n(%) Low energy fall High energy fall Road traffic accident Contact sport injury Other Missing			
Type of injury n(%) High-energy trauma Low-energy osteoporotic **Vertebrae involved n(%)** T10 T11 T12 L1 L2			
Previous back problems, n(%) Yes No **If yes, what was it?** Previous fracture Diagnosis of osteoporosis Other Missing			

Table Two: ODI

	Surgery Arm (n=)	Non-operative Arm (n=)	Overall (n=)
Pre-injury (collected at baseline) (n=) Mean (SD) Median (min, max) **Disability category, n(%)** Minimal disability Moderate disability Severe disability Crippled Bed-bound			

Baseline (n=) Mean (SD) Median (min, max) **Disability category, n(%)** Minimal disability Moderate disability Severe disability Crippled Bed-bound **Month 3 (n=)** Mean (SD) Median (min, max) **Disability category, n(%)** Minimal disability Moderate disability Severe disability Crippled Bed-bound **Month 6 (n=)** Mean (SD) Median (min, max) **Disability category, n(%)** Minimal disability Moderate disability Severe disability Crippled Bed-bound			

Table Three: VAS

	Surgery Arm (n=)	Non-operative Arm (n=)	Overall (n=)
Baseline (n=) Mean (SD) Median (min, max) **Month 3 (n=)** Mean (SD) Median (min, max) **Month 6 (n=)** Mean (SD) Median (min, max)			

Table Four: SF-12

	Surgery Arm (n=)	Non-operative Arm (n=)	Overall (n=)
Pre-inury (collected at baseline) (n=) **PCS-12** Mean (SD) Median (min, max) **MCS-12** Mean (SD) Median (min, max) **Month 3 (n=)** **PCS-12** Mean (SD) Median (min, max)**MCS-12** Mean (SD) Median (min, max) **Month 6 (n=)** **PCS-12** Mean (SD) Median (min, max)**MCS-12** Mean (SD) Median (min, max)			

Figure one: CONSORT diagram