# Statistical Analysis Plan

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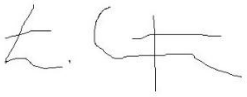
| **Chief Investigator** | **Edd Carlton** |  | **12 May 2025** |

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# 1. Introduction

## 1.1 Scope of the document

The statistical analysis plan (SAP) for the COMITED study has been written in accordance with Bristol Trials Centre (BTC) standard operating procedures, the CONSORT statement,[1] and International Conference on Harmonisation (ICH) Statistical Principles for Clinical Trials E9 (www.ema.europa.eu). The plan covers all final statistical analyses to be performed for reporting in the primary results paper. Any further analyses of the COMITED data are beyond the scope of this plan, but would be expected to follow the same principles of best practice.

This plan has been informed by version 7.0 of the study protocol (23rd July 2024). However the current COMITED study protocol should be consulted for all details of the study other than the statistical plan. A journal version of the study protocol is available.[2]

Revisions to this plan must be enacted before the data have been released for analysis and will be justified in Section 7. Any deviations from this plan in the published primary analysis will be highlighted and justified in the publication.

## 1.2 Background of study

### 1.2.1 Study timelines

This project (contracting) started on the 1st October 2021. The project duration was expected to be 36 months, through to 30 September 2024.

Due to recruitment challenges, an extended recruitment period was agreed to by the funding body (NIHR-HTA) on 07 June 2024, with an updated project end date of 31 July 2025 (revised duration of 46 months). We estimate that this will allow us to recruit at least 380 participants with complete primary outcome data, which will allow us to demonstrate true non-inferiority of conservative management of traumatic pneumothoraces compared to usual care, with 90% power (i.e. the limit of a one-sided 97.5% confidence interval falling within a non-inferiority margin of 10%). This approach is supported by our trial oversight committees and Patient and Public Involvement (PPI) group, who considered 10% to be the maximum acceptable difference in subsequent pleural interventions in the intervention arm, in comparison with the control arm.

To allow the project to end in July 2025, the follow up period will be truncated by five months; therefore, only primary outcome data at day 30 will be collected for the final participants. It is estimated that we will not obtain 3-month follow up data for approximately 34 participants and not obtain 6-month follow up data for approximately 85 participants.

### 1.2.2 Study rationale

We estimate, from our prior observational and survey work, that around half of patients admitted to hospital with traumatic pneumothoraces will be treated with the insertion of a chest drain.[3, 4] Current guidelines advise chest drain insertion for any traumatic pneumothorax, although very small pneumothoraces can be managed with observation at the treating physician's discretion. For patients with very large pneumothoraces, chest drains can reduce the risk of cardiorespiratory compromise.[5] However, there remains a large proportion of patients in whom there is clinical

uncertainty as to whether an immediate chest drain is required.[3] Insertion is usually done in the emergency department (ED) and is one of the most invasive procedures undertaken outside of an operating theatre. Chest drains carry a high risk of complications such as bleeding and infection, which occur in 15-30% of patients.[6] There is no robust evidence to inform practice, and the default to invasive treatment may result in avoidable pain, distress and complications.

### 1.2.3 Aims and objectives

The COMITED randomised controlled trial addresses the overall study question "*is initial conservative management of significant traumatic pneumothoraces non-inferior to invasive management in terms of subsequent emergency pleural interventions (primary outcome), complications, pain, breathlessness, and quality of life?*". Specific study objectives are:

- To establish if initial conservative management is non-inferior to invasive management regarding subsequent emergency pleural intervention over 30 days (or until death if sooner).
- To determine whether conservative management improves health-related quality of life and other patient reported outcomes (PROMs).
- To determine the clinical and cost effectiveness of conservative management versus invasive management of traumatic pneumothoraces by measuring resource use, mortality and costs over the six months following injury.
- To assess the acceptability of initial conservative management to patients and clinicians.

### 1.2.4 Study governance

COMITED is registered at www.isrctn.com/ISRCTN35574247.

The conduct and reporting of COMITED has been overseen by a Trial Steering Committee and a Data Monitoring Committee (DMC).

# 2. Study methods

## 2.1 Design

Multi-centre, parallel group, individually randomised controlled **non-inferiority trial** with an internal pilot, economic evaluation and integrated qualitative study.

## 2.2 Consent procedures

When an eligible patient does not have capacity to provide informed consent, enrolment will take place under an emergency research protocol, with informed consent to be sought once the participant regains capacity or advice sought from a consultee if the participant does not regain capacity within seven days. **These participants may complete baseline PROMs up to seven days after randomisation, or may not complete PROMs at baseline**, and may decline further involvement in the research on regaining capacity.[7]

## 2.3 Randomisation

Participants are allocated in a 1:1 ratio to either “initial conservative management” (intervention group) or “chest drain insertion in the ED” (control group: invasive management). Randomisation is carried out using an online system, and minimised by three factors: study site, ventilation status, and mechanism of injury (blunt vs. penetrating), as established at the point of randomisation. **One or both of a participant’s lungs may be eligible and included in the study; when both lungs are included, both follow the participant’s randomised allocation for treatment.**

## 2.4 Sample size

PPI contributors suggested that an increase of 5 to 10% in subsequent emergency pleural intervention would be acceptable compared to usual care, given the reduction in the overall number of chest drains in the intervention group. These views informed the pre-specification of a non-inferiority margin of 7.5% higher in the intervention (conservative management) group compared to the control group (i.e. no more than 17.5% in the intervention group if the rate in the control group is 10%).

If the incidence of the primary outcome in both study groups is 10%, a sample size of 674 (337 in each group) will allow non-inferiority to be concluded with 90% power when comparing a one-sided 97.5% confidence interval, for the absolute difference in primary outcome incidence, to a non-inferiority margin of 7.5%. Allowing for 10% loss to follow-up increases the total sample size to 750 participants.

Once it became clear that the recruitment target of 750 participants would not be met, agreement was reached with the funder and oversight committees that a revised target of 400 participants would allow non-inferiority to be concluded with a margin of 10%.

## 2.5 Blinding

Of those research staff involved with the day-to-day conduct of the study, only those evaluating outcomes for the analyses can be blinded to treatment group allocation. Members of the Trial

Management Group, including the supervisory statistician, will be blinded throughout the study. The trial statistician will be unblinded during the study, to be able to prepare reports for the closed DMC meeting.

## 2.6 Data sources

Quantitative clinical data will be collected by medical record review and recorded onto case report forms (CRFs). Participants will be asked to complete several patient reported outcome measures, using paper or online formats, at baseline (when possible), and at 30 days, three months, and six months post-randomisation.

## 2.7 Schedule of assessments and outcome data collection

Baseline: Socioeconomic data, clinical history, PROMs: Brief Pain Inventory, MRC dyspnoea scale, EQ-5D-5L.

30 days: Pleural interventions, complications of pleural interventions, days of pleural drainage, length of stay, ED attendances, unplanned readmissions, pneumothorax or chest injury related mortality since randomisation, PROMs as for baseline, plus the Impact of Events scale.

3 months: PROMs as for 30 days.

6 months: PROMs as for 30 days, all-cause mortality since randomisation.

# 3. Populations

## 3.1 Study population

Adults presenting with traumatic pneumothoraces. The inclusion and exclusion criteria are detailed in the study protocol, with the following being a summary.

### 3.1.1 Inclusion criteria

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

- Patients presenting with traumatic pneumothorax / pneumothoraces
- Aged, or believed to be aged, 16 years and over, and
- In whom the treating clinician(s) believes either a chest drain or conservative management is a suitable initial treatment option.

### 3.1.2 Exclusion criteria

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

- Treating clinician(s) believes injuries are incompatible with life
- Patient in respiratory arrest
- Haemothorax requiring a chest drain in the opinion of the treating clinician(s)
- Clinical or imaging evidence of tension pneumothorax in either lung at the point of randomisation
- Prisoners

## 3.2 Analysis populations

### 3.2.1 Intention-to-treat population

All summaries and analyses, including complications, will be conducted on the intention-to-treat (ITT) population. The ITT population will consist of all participants, included according to their allocation to the intervention or control group, regardless of whether they are subsequently found to be ineligible, prematurely discontinue their allocated management, or are otherwise protocol deviators.

### 3.2.2 Per-protocol population

The primary ITT comparison is made on the basis of non-inferiority. As this analysis can be considered “anti-conservative” (non-inferiority is more likely to be demonstrated if the allocated groups become more similar due to a high proportion of participants failing to adhere to their intervention) we will conduct a sensitivity analysis with the per protocol population who adhered to the clinical management protocol in their allocated group.

# 4. Statistical analyses and report content

## 4.1 General considerations

The data will be analysed according to the ITT principle, such that each participant's data will contribute to the findings for the group they were allocated to, irrespective of any subsequent diagnostic information or the treatment actually received. Primary and secondary analyses will be based on observed data (acknowledging that this deviates from ICH E9), with the effect of any missing data on the primary analysis explored in sensitivity analyses. Reporting of the study methodology and results will be according to the CONSORT guidelines.

The conclusions will be focused on the findings of the analysis of the primary outcome measure. No formal adjustment will be made to the type I error rate with regards to the number of secondary outcome measures, but consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

In general, for each outcome measure, appropriate summary statistics will be presented for each allocated group, plus an estimate of the difference between allocated groups with 95% confidence interval and p-value.

Any baseline questionnaire data collected more than 24 hours after randomisation will be presented as summary statistics, but will not be included in regression models.

As reported in section 1.2.1, some participants recruited later in the study will not be invited to complete the three month and/or six month measures. This administrative censoring will be "missing completely at random" and will not cause bias in a complete cases analysis.

## 4.2 Definition and derivation of the outcomes

The primary outcome is the need for one or more subsequent emergency pleural interventions (such as chest drain insertion, re-insertion, video-assisted thorascopy, thoracotomy) in the eligible lung(s) within 30 days of randomisation. Secondary outcomes are as follows:

<u>Source: routinely collected clinical data</u>

All pleural interventions (including chest drain insertion in the ED undertaken as standard care) up to 30 days.

All complications of pleural interventions up to 30 days.

Total days of pleural drainage up to 30 days.

Total length of stay (hospital, critical care and readmission) up to 30 days.

Mortality, pneumothorax or chest injury related, up to 30 days.

All-cause mortality at six months.

Source: PROMs

Brief Pain Inventory.[8]

MRC breathlessness scale.[9]

Impact of Events Scale – Revised.[10]

EQ-5D-5L.[11]

The Brief Pain Inventory has two subscales, the Pain Severity Score and the Pain Interference Score, both of which range from 0 (least severe / interference) to 10 (most severe / interference).[8] The Pain Severity Score is based on four items, asking the respondent to rate the worst, least, and average pain in the preceding week, plus current pain levels on a 0 (anchor: no pain) to 10 (anchor: pain as bad as you can imagine) Likert scale. The score is the mean of the four items. The Pain Interference Score is based on six items, asking whether pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Each is rated on a 0 (anchor: does not interfere) to 10 (anchor: completely interferes) Likert Scale, with the subscale score being the mean of the six items.

Participants complete the MRC breathlessness scale by selecting one of five statements as best describing their condition, the statements ranging from no disability (Grade 1: Not troubled by breathlessness except on strenuous exercise) to almost complete incapacity (Grade 5: Too breathless to leave the house, or breathless when undressing).[9]

The Impact of Events Scale (Revised) comprises 22 questions (e.g. “I had trouble staying asleep”) with the respondent directed to “Please read each item and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS”. Responses are given on a five point scale (0: not at all, 1: a little bit, 2: moderately, 3: quite a bit, 4: extremely), the total score being the mean rating from all non-missing items. We will not report the three subscale scores: avoidance, intrusion, and hyperarousal. A total score of 24 or above has been suggested to indicate a clinically significant traumatic stress response, with a score above 33 suggesting the individual may be diagnosed with “probable post-traumatic stress disorder”.[10]

The EQ-5D-5L will be utilized in the health economic analysis.[11]

## 4.3 Analysis of the outcomes

The incidence of the primary outcome measure (one or more emergency pleural interventions in the 30 days following randomisation) will be presented as observed (number of participants with a primary outcome divided by the number of participants in the allocated group) and in addition, if censoring exceeds 5% of the sample, using an approach such as Kaplan Meier (Table 2). **Participants who died due to pneumothorax or chest injury without a preceding emergency pleural intervention will be counted as having had a primary outcome event on the day of death.** The intervention effect will be estimated and presented as an unadjusted absolute difference in incidence between conservative management and control groups, with the limit of the one-sided 97.5% confidence interval. If the confidence interval is within a 10% non-inferiority bound, conservative management will be concluded to be non-inferior to usual care. If non-inferiority is demonstrated, evidence from the risk difference, two-sided 95% confidence interval,

and p-value, will be presented to allow inference about the superiority of conservative management compared to usual care.

Analysis of secondary outcomes will utilise appropriate regression models, with covariates distinguishing the allocated groups, **whether the participant had a penetrating injury, and whether the participant required ventilation at recruitment (minimisation variables)** (Table 3). For the analysis of Pain Intensity and Pain Interference, the corresponding baseline measure will be included as a covariate, with a second covariate identifying those participants without a baseline measure.[12]

It is anticipated that the following regression models will be used:

Cox proportional hazards: Any pleural intervention within 30 days, days until completion of pleural drainage (censored at 30 days), days until hospital discharge (censored at 30 days), mortality due to pneumothorax or chest injury within 30 days (Table 3), all-cause mortality within six months (Supplementary Figure 3).

Ordinary least squares: Pain Severity, Pain Interference, Impact of Events, each at 30 days, (Table 3).

Ordered logistic: MRC Breathlessness Scale (Table 3).

Model assumptions will be checked graphically, and the effect of any deviation from assumptions checked in additional sensitivity analyses (e.g. dropping outlying values, adding terms to the model).

Summary statistics will be presented for the repeated measurements of each PROM (Supplementary Table 1). **A formal repeated measures (mixed effects) analysis will be conducted if completion remains above 75% (of those invited to complete the measures) at each time point.** Time of completion for this analysis will be treated as continuous, with the treatment effect interpreted as the average difference in means between the allocated groups over the six-month study period.

Complications of pleural interventions within 30 days will be tabulated, but without formal tests being conducted. The categories of complications described by Aho and colleagues will be presented separately (Supplementary Table 2).[13]

## 4.4 General content

### 4.4.1 Participant flow

The CONSORT flowchart will be used to summarise the flow of participants from screening until follow-up throughout the course of the study (Figure 1 and Supplementary Figure 1). This will include the number of:

### 4.4.2 Baseline measures

Summary statistics for demographic information and clinical measures taken at baseline will be presented by allocated group (Table 1).

### 4.4.3 Sensitivity analyses

It is expected that missing primary outcome data will be very limited and largely due to participants withdrawing from the study. If missing primary outcome data exceed 10%, we will establish, amongst those with these data missing, the required incidence of emergency pleural procedure in the patients allocated to the intervention group, for non-inferiority to no longer be supported (Supplementary Figure 2).

If adherence to random allocation is below 90%, the primary analysis will be repeated with the per protocol population (Table 2).

## 5. References

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8. Tan, G., et al., *Validation of the Brief Pain Inventory for chronic nonmalignant pain.* J Pain, 2004. **5**(2): p. 133-7.
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12. Groenwold, R.H., et al., *Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis.* CMAJ, 2012. **184**(11): p. 1265-9.
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## 6. Glossary

| | |
|---|---|
| BTC | Bristol Trials Centre |
| CRF | Case Report Form |
| DMC | Data Monitoring Committee |
| ED | Emergency Department |
| ICH | International Conference on Harmonisation |
| IQR | Inter-Quartile Range |
| ITT | Intention To Treat |
| MRC | Medical Research Council |
| NIHR-HTA | National Institute for Health and Care Research – Health Technology Assessment Programme |
| PPI | Patient and Public Involvement |
| PROMs | Patient Reported Outcome Measures |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |

## 7. Revision history

| Version number | Revision date | Justification for revision |
|---|---|---|
| | | |

## 8. Outline tables and figures

**Table 1.** Baseline demographic and clinical information

| | **Intervention: no chest drain (n = )** | **Comparison: chest drain (n = )** |
|---|---|---|
| Number older than 65 years (%) | | |
| Number male (%) | | |
| Number recruited at major trauma centre (%) | | |
| Number bilateral (%) | | |
| Mean Injury Severity Score (SD), n | | |
| Mean Clinical Frailty Score (SD), n | | |
| *Pneumothorax size:* | | |
| Number less than 2cm (%) | | |
| Number 2 to 5cm (%) | | |
| Number greater than 5cm (%) | | |
| Number without pre-hospital thoracostomy (%) | | |
| Number spontaneously ventilating (%) | | |
| Number blunt injury (%) | | |
| *Mechanism of injury:* | | |
| Road traffic accident (%) | | |
| Fall (%) | | |
| Stabbing or blow with weapon (%) | | |
| Other (%) | | |

**Table 2.** Primary outcome analysis

| | Intervention: no chest drain | Comparison: chest drain | Risk difference (95% confidence interval) |
|---|---|---|---|
| ITT primary outcome analysis | | | |
| *Sensitivity analyses:* | | | |
| Per protocol analysis* | | | |

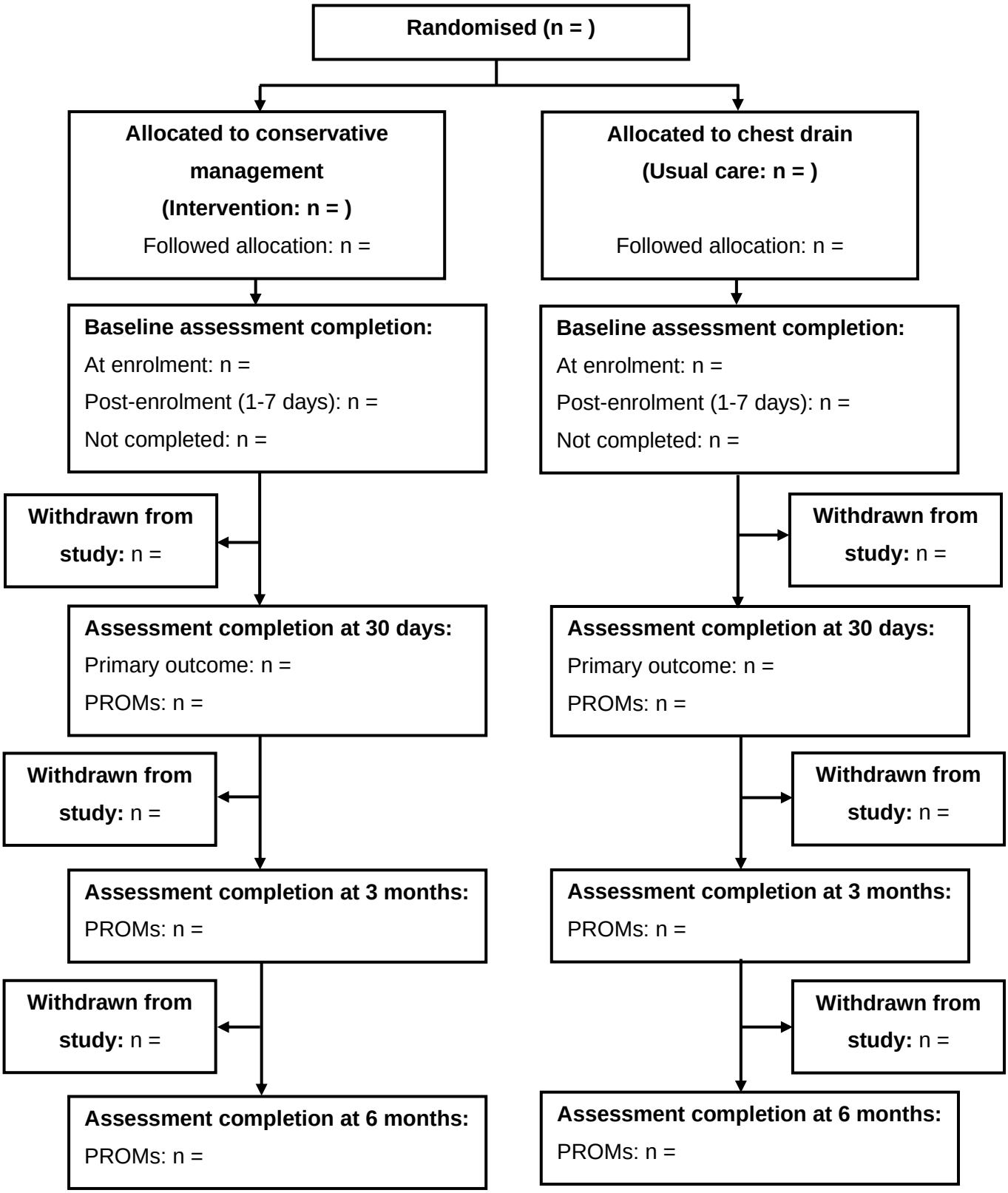
*If required.

**Table 3.** Secondary outcome analyses at 30 days

| | **Intervention: no chest drain** | **Comparison: chest drain** | **Treatment effect estimate* (95% confidence interval)** |
|---|---|---|---|
| | **Mean (SD), N** | **Mean (SD), n** | **Difference in means** |
| Pain severity | | | |
| Pain interference | | | |
| Impact of events | | | |
| | | | |
| MRC Breathlessness grade | **n (%)** | **n (%)** | **Odds ratio** |
| 5 (Severe impairment) | | | |
| 4 | | | |
| 3 | | | |
| 2 | | | |
| 1 (No impairment) | | | |
| | | | |
| | **Median (IQR), N** | **Median (IQR), N** | **Hazard ratio** |
| Days to drainage complete | | | |
| Days to hospital discharge | | | |
| | | | |
| | **Events/N (%)** | **Events/N (%)** | **Hazard ratio** |
| Any pleural intervention | | | |
| Mortality due to chest injury or pneumothorax | | | |

* Adjusted for penetrating injury and whether the patient required ventilation at recruitment

**Figure 1.** CONSORT flowchart, random allocation onwards



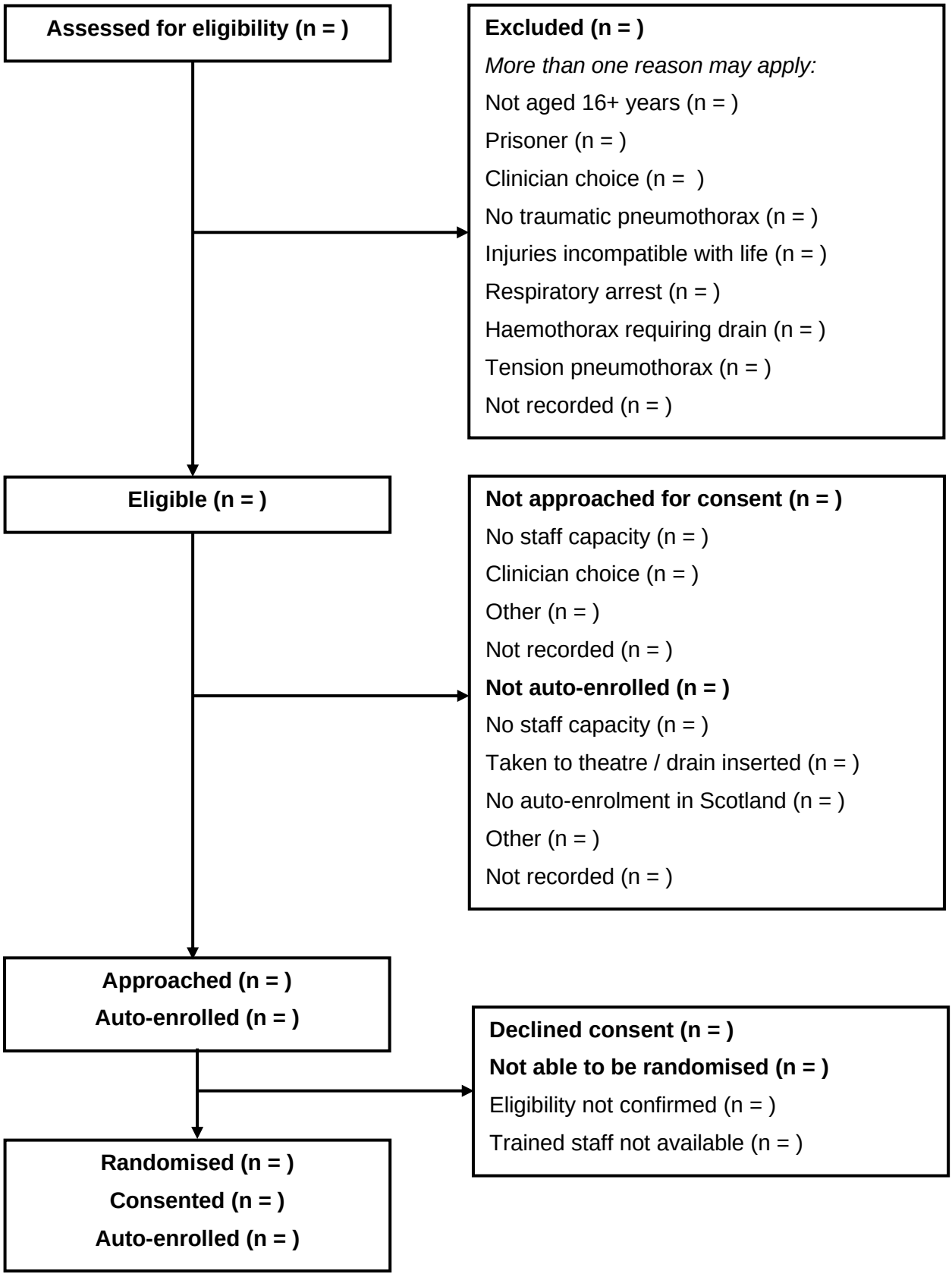
**Supplementary Table 1.** Summary statistics for repeated measures of the PROMs

| | **Intervention: no chest drain (n = )** | **Comparison: chest drain (n = )** |
|---|---|---|
| | Mean (SD), N | Mean (SD), N |
| *Pain severity:* | | |
| Baseline | | |
| 30 days | | |
| 3 months | | |
| 6 months | | |
| *Pain interference:* | | |
| Baseline | | |
| 30 days | | |
| 3 months | | |
| 6 months | | |
| *Impact of events:* | | |
| 30 days | | |
| 3 months | | |
| 6 months | | |
| MRC Breathlessness grade | Median (IQR), N | Median (IQR), N |
| Baseline | | |
| 30 days | | |
| 3 months | | |
| 6 months | | |

**Supplementary Table 2.** Frequency of complications, total and according to the Aho et al categories

| | **Intervention: no chest drain (n = )** | **Comparison: chest drain (n = )** |
|---|---|---|
| Number of participants with one or more complications | | |
| Number of participants with one or more INSERTIONAL complications | | |
| Number of participants with one or more POSITIONAL complications | | |
| Number of participants with one or more REMOVAL complications | | |
| Number of participants with one or more INFECTIVE/IMMUNOLOGIC complications | | |
| Number of participants with one or more FAILURE complications | | |
| Number of participants with one or more FATAL complications | | |

**Supplementary Figure 1.** CONSORT Flowchart, up to random allocation **(categories are examples)**



**Supplementary Figure 2:** Risk differences (95% confidence intervals) for the primary outcome measure with missing data imputed according to a range of strengths of association between allocated group and the risk of an outcome event amongst the missing values.

**Supplementary Figure 3**: All-cause mortality by allocated group (Kaplan-Meier estimates) (Hazard ratio, 95% confidence interval will be included).