# MSK-ICU

Evaluating the musculoskeletal health state of Intensive Care Unit Survivors:
The MSK-ICU Study

# Statistical Analysis Plan

Version 1.0 – 25th May 2023

Based on version 4.0 (4th December 2022) of protocol

| Name | Title | Role | Signature | Date |
|---|---|---|---|---|
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# Contents

## INTRODUCTION

This document details the proposed statistical analysis and presentation of the results for the main paper(s) reporting the findings from *the NIHR funded Evaluating the musculoskeletal health state of intensive care unit survivors (MSK-ICU) study.* 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, 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 modelling and reporting the development and validation of the proposed prognostic model.

Any deviations from the statistical analysis plan will be described and justified in the final report of the study. An identified, appropriately qualified and experienced statistician will support the Chief Investigator in conducting the analysis, as well as ensuring the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

The structure and content of this document provides sufficient detail to meet the requirements identified by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

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### 1.2 Changes from previous version of SAP

Not applicable as this is the first version of SAP based on Protocol version 4.0 4Dec2022.

## BACKGROUND

The number of admissions to intensive care units (ICU), complexity of illness and cost of critical care is increasing over time. This is representative of both an aging critical care population presenting with a variety of pre-existing co-morbidities, and an increase in survival rates due to improvements in ICU services and delivery **[Kaukonen et al., 2000]**. Survivors of critical illness frequently experience long-term physical impairment, persistent exercise limitation and decreased health-related quality of life (QoL) **[Herridge et al., 2011]**. The subsequent socioeconomic burden of critical illness is high, with significant healthcare utilisation after discharge from hospital **[Ruhl et al., 2017]**. Rates of return to employment following admission to ICU are also affected, with up to 31% of patients not returning to work within five years of ICU admission **[Kamdar et al., 2018].**

Multiple recent studies investigating rehabilitation interventions after ICU and hospital discharge have failed to demonstrate positive primary outcomes for patient reported physical function and exercise capacity **[McWilliams et al., 2016, McDowell et al., 2017, Battle et al., 2019]**. The interventions evaluated in these studies are based on the successful group exercise programmes used in cardiac and pulmonary rehabilitation, constituting cardiopulmonary and general strengthening exercises. It is unclear to what extent general weakness and decreased exercise capacity contribute to poor outcomes and thus explanatory power for the lack of effectiveness of these interventions. If other physical problems are found to influence function and QoL, more effective rehabilitation interventions could be designed and evaluated.

Musculoskeletal (MSK) conditions are wide ranging and include problems affecting bone, muscle and joints. They are the leading cause of pain and disability in the UK with 25% of the population affected **[NIHR, 2018]**. They are characterised by pain and loss of function and can diminish QoL and impact on family and social relationships. MSK conditions also have a significant socioeconomic impact. They are the second leading cause of sickness absence at work, with 30.8 million working days lost in the UK in 2016 due to MSK problems **[Comer, 2016]**.

Given the rates of muscle mass loss of up to 20% in the first week of ICU admission **[Puthucheary et al., 2013]**, it is reasonable to expect that patients will subsequently present with MSK complications after discharge from ICU. Therefore, it is possible that long term MSK complications are contributing to poor physical function, QoL and return to work in ICU survivors.

This potential source of long-term disability in ICU survivors is under-investigated. A scoping review of MSK complications following critical illness highlighted several studies investigating MSK health after hospital discharge **[Gustafson et al., 2021]**. Most studies evaluated a single aspect of MSK health, with peripheral muscle weakness, chronic pain and abnormal neuromuscular function being the most assessed and reported outcomes. High prevalence of MSK complications were reported with the shoulder identified as the most commonly affected joint. None of the studies have evaluated the overall MSK health state of ICU survivors using MSK specific patient reported measures and work metrics.

Despite individual MSK complications being prevalent in ICU survivors, the impact of their MSK health state on physical function and QoL is unknown. To develop successful future post-ICU rehabilitation interventions more detail regarding the reasons underlying poor physical function need to be established.

Therefore we primarily aim to determine and characterise the MSK health state of ICU survivors six months following admission to ICU. Secondarily we will explore prognostic factors and presentations for impairment, structure and function.

## OBJECTIVES

### 3.1 Primary Objectives

To quantify the MSK health state using the MSK Health Questionnaire (MSK-HQ) and assess its relationship with QoL, employment, anxiety and depression, and symptoms of post-traumatic stress disorder (PTSD).

### 3.2 Secondary Objectives

To identify prognostic factors for a lower MSK-HQ score after critical illness.

To characterise the specific MSK complications experienced by patients using a standardised comprehensive MSK assessment.

To evaluate patient mobility and upper limb function, and the extent of the relationship to muscle structure and function in those patients with poor MSK health state.

## METHODS

### 4.1 Study design

The MSK-ICU study is a multicentre, prospective, longitudinal cohort study exploring the MSK health state of ICU survivors. Data collection is split into a primary study using a telephone follow-up questionnaire, and two sub studies involving in-person assessments.

### 4.2 Study population

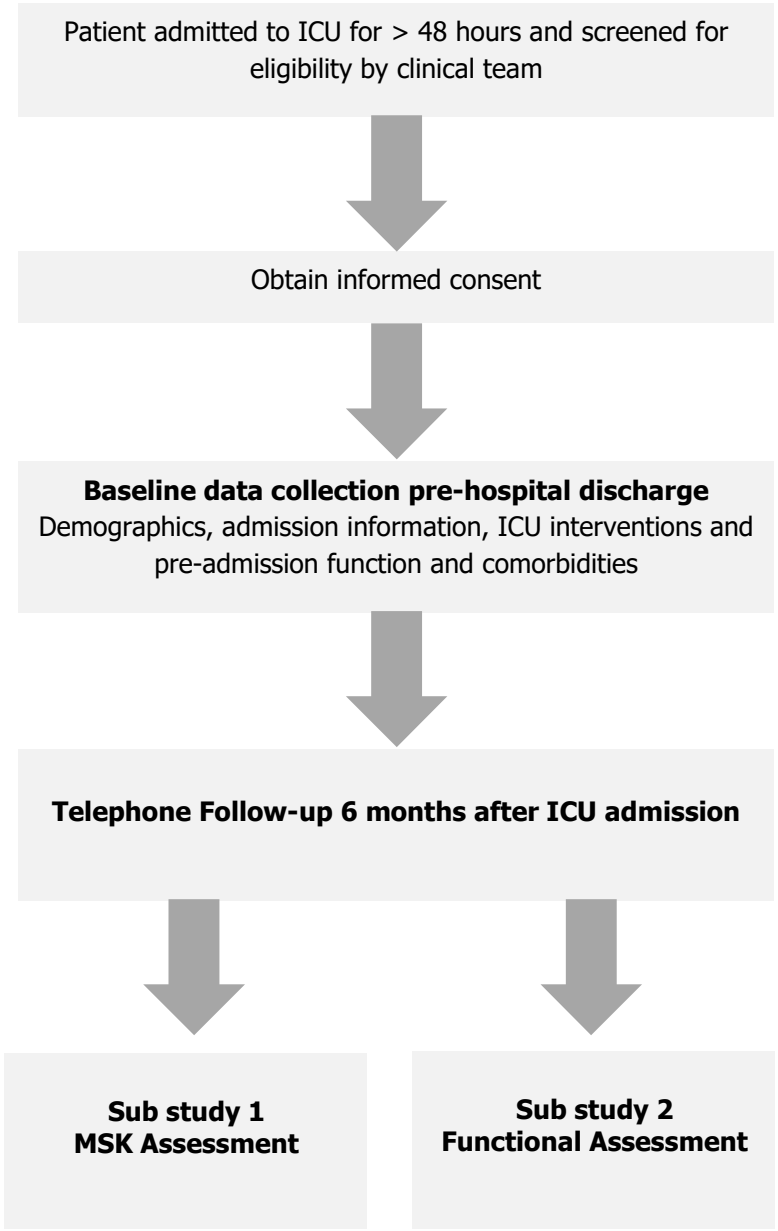
**Inclusion criteria**

- Age 18 years and older
- Admitted to an ICU for >48 hours

**Exclusion criteria**

- Patients who are judged to lack capacity at the time of consent as defined by the Mental Capacity Act (2005).
- Proven or suspected primary brain pathology, spinal cord injury or other neuromuscular disease resulting in permanent or prolonged weakness.
- Admitted to ICU with musculoskeletal complications or trauma.
- Patients who have a palliative diagnosis/treatment pathway.
- Patients who were dependent for activities of daily living in the month prior to current intensive care unit admission (gait aids acceptable).
- Prisoners.
- Patients with no fixed abode.
- Patients who are unable to communicate clearly in English over the telephone for 20 minutes.
- Patients refusing consent.

### 4.3 Study time points




### 4.4 Outcome measures

The primary outcome measure is the MSK-HQ which is a measure of overall MSK health state.
Other outcome measures collected make up the recommended core outcome set for ICU follow-up studies **[Dinglas et al., 2020]**, including: European Quality of Life: 5 Dimensions (EQ-5D-5L) utility score, Hospital Anxiety and Depressions Scale (HADS), Impact of Events Scale-Revised (IES-R), and Employment questionnaire.

### 4.5 Data collected

A complete list of variables collected in the MSK-ICU study is available in **Appendix 1**.

### 4.6 Sample size

The sample size calculation is based on the analysis requiring the largest sample size, which is the secondary objective of identifying prognostic factors for the development of a lower MSK-HQ score at six months after admission to ICU. Based on a local case mix data for the participating ICUs, approximately 1,700 admitted patients have an ICU length of stay greater than 48 hours and are discharged to a ward within the hospital annually. Approximately 400 patients would be ineligible for participation in the study, and when accounting for an inpatient mortality of 7%, approximately 1,200 eligible patients would be expected to survive to discharge from hospital. For the purpose of developing a prognostic model, the MSK-HQ score will be treated as a continuous variable. There are 15 potential baseline prognostic factors identified. Based on this number of predictors and assuming an approximately normal distribution of residuals, the minimum sample size required to estimate a multiplicative margin of error of 0.1 would be 249 individuals.(35) Allowing for a 25% loss to follow-up, it is necessary to recruit 332 participants. This sample size and number of predictors would also ensure the estimation of a shrinkage factor ≥ 0.9 and a difference between apparent and adjusted $R^2$ ≤ 0.02, even with a moderate anticipated $R^2$ of 0.6.

## DESCRIPTIVE ANALYSIS

### 5.1 Descriptive statistics

#### *5.2.1 Baseline characteristics of the participants*

Baseline characteristics of the sample will be described using either means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables (depending on data distribution). Categorical variables will be described using frequencies and percentages. No formal statistical test will be performed.

#### *5.2.2 Outcome measures*

The mean (SD) and median (IQR) MSK-HQ score for the sample will be presented. Additionally, the number of participants reporting musculoskeletal complications will also be presented. Each binary or categorical predictor will be tabulated against outcome to check for (almost) empty cells, in which case the predictor variable might be excluded if there are no categories that could reasonably be collapsed.

#### *5.2.3 Predictor variables*

For all potential predictor variables, the completeness of baseline data will be presented overall and separately according to the presence or absence of outcome symptoms. The frequency of each category and the percentage of outlier values for continuous variables will also be tabulated.

## MODEL DEVELOPMENT

Even though the aim of the study is not to formally develop a prognostic model, but rather to identify potentially important predictor factors of MSK health state, we will employ a prognostic model development framework to ensure the robustness of the procedures.
The following procedures will be applied for the development of the two prognostic models. Information from all subjects in the MSK-ICU study will be used to develop the two predictive models proposed in this SAP. Both models will include baseline variables to predict MSK health status in terms of MSK-HQ score and self-reported MSK complications (yes/no). The difference between the models will be the outcomes definition (i.e., continuous or binary).

### 6.1 Definition of outcomes

**Outcome for Model 1**

- MSK-HQ score (0-56) – treated as continuous

**Model 2**

- MSK complication (yes/no) – binary

### 6.2 Definition of predictor variables

The pre-selected variables that we will explore as potential predictors of poor outcome after ankle sprain are listed in **Table 1**:

| Type | Variable name | Categories / units (range) |
|---|---|---|
| Binary | Sex | Male, female |
| | Active MSK problem | Yes, No |
| | Admission diagnosis | Yes, No |
| | Sepsis | Yes, No |
| | Prone | Yes, No |
| | Neuromuscular Blocking Agents | Yes, No |
| | Rehabilitation in ICU | Yes, No |
| | Mechanical ventilation | Yes, No |
| Ordinal | Clinical Frailty Scale | Score (1-9) |
| | Functional comorbidity index | Score (0-18) |
| | ICU Mobility Scale | Score (0-10) |
| | Derived index of Multiple Deprivation | Score (1-10) |
| Continuous | Age | Years |
| | APACHE II | Score (0-71) |
| | Medical Research Council Sum Score (MRCSS) | Score (0-60) |
| | Time to first rehabilitation | Days |
| | ICU Length of stay | Days |
| | Hospital length of stay | Days |

### 6.3 Predictor analysis

Though there is currently no consensus on the ideal way of developing a prognostic model, a transparent process will be used **[Collins et al., 2015]**, implementing appropriate statistical methods and adhering to current methodological recommendations **[Moons et al., 2015]**.

### *6.3.1 Before Modelling*

The correlation between predictors will be examined in order to investigate whether highly correlated predictors can be omitted prior to the multivariable modelling. Highly correlated predictors will not be included together in the model. The decision about which predictor will be kept in the model will take into account the individual and adjusted predictive ability of each variable, and the predictor with higher face-validity will be included. Missing data will also be examined to exclude any predictors with substantial amounts of missing data.

### *6.3.2 During Modelling*

For the continuous outcome a linear regression modelling approach will be used, with the MSK-HQ score as the response variable. For the binary outcome of self-reported presence or absence of musculoskeletal problem a logistic regression modelling framework will be undertaken with the logit probability of an adverse outcome as the dependent (response) variable. Both linear and logistic regression models will be fitted using a statistical package that allows the data analysis to be performed with a structured and reproducible code (for example, the Stata *regress* and *logit* procedures).

The predictors described in 6.2 will be included as independent variables in the model. A backwards elimination (stepwise) procedure will be used to identify which of the candidate predictor variables will be included in the final prognostic models, with $p < 0.157$ (equivalent to Akaike Information Criterion) conservatively taken to warrant inclusion and prevent overfitting. Continuous predictors will be kept as continuous in the model (rather than, say, dichotomised), to avoid any loss of prognostic information. Non-linear relationships between predictors and outcomes will also be investigated using fractional polynomials and the multivariable fractional polynomials.

### *6.3.3 After modelling*

Once a final model is fitted model performance characteristics, including the adjusted $R^2$ (for linear regression models), c-index (for logistic regression models), and assessment of calibration for all developed models will be reported.

### 6.4 Assumption checks

Continuous predictor variables will be checked for normality using graphical methods. Influence of individual data points will be assessed by plotting leverage residuals against fitted data. Deviance residuals will be used to identify outliers.

If any outliers or influential data points are found, a sensitivity analysis to check the robustness of the model will be performed (see **section 7.4**).

## GENERAL ISSUES FOR STATISTICAL ANALYSIS

### 7.2 Methods for handling missing data

Although large amounts of missing variable data are not expected, some will inevitably occur, with not all individuals providing data for all variables of interest. This could be because some symptoms are not usually asked by clinicians and so not recorded in notes. Data omission rarely occurs completely at random, but rather selectively (i.e., selective missing data) **[van Zaane, 2010]**. A comparison of characteristics between subjects with and without missing values will therefore be done to check whether missing data indeed was not at random.

If missingness of data is indeed related to other observed variables, it is increasingly acknowledged that standard “complete case analyses” not only reduces the sample size, but also can lead to biased results in the

presence of selectively missing data; since the individuals with missing data are then not a random subset of those with fully observed data **[Janssen, 2010]**. Simply excluding subjects with missing data would thus not solve a problem but create selection bias, as the 'intention to test' principle (in conformity randomized trials) is violated.

Therefore, to conform to current guidelines **[Moons et al., 2015]** multiple imputation for all subjects with at least one missing value (using the *mi impute* function in Stata, for example) will be used. The imputation models will be made using the chained equations procedure and include all available observed characteristics and the outcome. The regression parameter estimates plus corresponding standard errors obtained from the prognostic modelling analyses of the multiple imputed datasets will be combined using Rubin's Rules **[Rubin, 2004]**. If the models will not converge, some predictor preselection will be done based on clinical expertise and subject matter.

### 7.3 Method for selecting predictors and variables to adjust for

As discussed in **Section 4.6**, the MSK-ICU study dataset will allow the examination of 15 baseline candidate predictor variables for inclusion in the prognostic models. For this purpose, a priori the list of 26 available variables (see **Appendix 1**) was reduced to those 17 variables considered to have potential prognostic ability (see **section 6.2**, **Table 1**), based on clinical knowledge as well as previously published data **[Battle et al., 2013, Pfoh et al., 2016, Koster-Brouwer et al., 2020, Probert et al., 2021]**. The unadjusted and adjusted odds ratio for each variable will be examined and the identification of the most important will be based on:

1) their effect size (larger odds ratios/β coefficients preferred);

2) statistical significance (smaller p-values preferred);

### 7.4 Method for handling outliers

Outliers will be identified by plotting box plots of each continuous variable. Clinical judgment is needed to assess if the outlier could be a true possible value. When running the final model, a sensitivity analysis will be performed by excluding any outlying values and checking the robustness (accuracy) of the model to these.

### 7.5 Derived and computed variables

Any derived or computed variables will be documented in the analysis programs.

## REPORTING

The primary objective of quantifying the MSK health state of ICU survivors will be reported according to the STROBE statement **[Vandenbroucke et al, 2014]**. The secondary objective of describing prognostic factor identification and internal validation will be reported according to the TRIPOD Statement [**Collins et al**, **2015**].

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## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| APACHE II | Acute Physiology and Chronic Health Evaluation 2 |
| AUC | Area Under the Curve |
| ROC | Receiver Operating Characteristic |
| BMI | Body Mass Index |
| CSM | Centre for Statistics in Medicine |
| DN4 | Douleur Neuropathique 4 Questions |
| EPV | Events Per Variable |
| EQ-5D-5L | European Quality of Life: 5 Dimensions |
| FABQ | Fear Avoidance Beliefs Questionnaire |
| GCP | Good Clinical Practice |
| HADS | Hospital Anxiety and Depression Score |
| IES-R | Impact of Events Scale - Revised |
| IDI | Integrated Discrimination Improvement |
| ICU | Intensive Care Unit |
| ICH | International Conference of Harmonisation |
| IQR | Interquartile range |
| MRCSS | Medical Research Council Sum Score |
| MSK | Musculoskeletal |
| MSK-HQ | Musculoskeletal Health Questionnaire |
| NHS FT | National Health Service Foundation Trust |
| NRI | Net Reclassification Improvement |
| OCTRU | Oxford Clinical Trials Research Unit |
| OxINMAHR | Oxford Institute for Nursing, Midwifery and Allied Health Research |
| QoL | Quality of Life |
| PTSD | Post-traumatic stress disorder |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOP | Standard Operational Procedure |
| STROBE | Strength |
| UK | United Kingdom |
| VAS | Visual Analogue Scale |

## DOCUMENT HISTORY

| Version number Issue date | Author | Significant changes from previous version |
|---|---|---|
| V1.0_5May2023 | Owen Gustafson | Not applicable as this is the 1st issue. |

## APPENDIX 1 – COMPLETE LIST OF BASELINE VARIABLES

**Baseline data collection**

- Age
- Sex
- Ethnicity
- Derived index of multiple deprivation
- Weight
- Height
- BMI
- Presence of a pre-existing active MSK problem
- Clinical Frailty Scale
- Functional Comorbidity Index

**ICU characteristics**

- APACHE II
- Admission diagnosis (medical/surgical)
- COVID-19 positive
- Admission type (emergency/elective)
- Mechanical ventilation (invasive for >12 hours, yes/no)
- Mechanical ventilation duration (hours)
- Neuromuscular blocking agents (additional to intubation)
- Steroids (a new course in ICU)
- Sepsis (proven or suspected infection with a SOFA score of ≥2 on ICU admission)
- Prone position (during invasive ventilation)
- Medical Research Council Sum Score (lowest recorded in ICU)
- Rehabilitation received in ICU (minimum movement to the edge of the bed)
- Day rehabilitation commenced in ICU
- ICU mobility scale (highest achieved within 48 hours prior to ICU discharge)
- ICU length of stay (days)
- Hospital length of stay (days)

## APPENDIX 2 – COMPLETE LIST OF OUTCOME VARIABLES

**Primary study – Telephone follow-up**

- History of traumatic MSK injury or fall since leaving hospital?
- Received physical rehabilitation for MSK problem since leaving hospital?
- Physical rehabilitation treatment details
- Any new medication since admission to ICU?
- Medication details
- Do you have an MSK problem?
- MSK problem details
- Any other concerns that haven't been discussed
- MSK-HQ score (including physical activity question)
- EQ-5D-5L
- John's Hopkins employment questionnaire (ever employed, employment situation pre-ICU, occupation, primary income earner pre-ICU, reason for unemployment pre-ICU, current employment situation, worked since leaving hospital, number of weeks from hospital discharge to return to work, primary income earner post-ICU, any changes in occupation, any changes in duties, ICU impact on work effectiveness, percentage change in earnings since ICU admission).
- HADS
- IES-R

**Substudy 1 – In-person MSK assessment**

- MSK injury or visited healthcare professional since primary study
- Injury or appointment details
- Red flags reported (yes/no)
- Highest pain severity in past 3 days (VAS 0-100)
- Pain location
- DN4 questionnaire
- Range of movement assessment upper and lower limb (full, limited, severely limited)
- Medical Research Council Sum Score
- Handgrip dynamometry (3 assessments and average)
- Knee extension dynamometry at $90^0$ flexion (3 assessments and average)
- MSK impairment description/comments
- Fear Avoidance Belief Questionnaire

**Substudy 2 – In-person functional assessment**

- Chest pain, dizziness or shortness of breath at rest
- Symptom details
- $SpO_2$
- Pulse
- Visited healthcare professional since last contact
- Healthcare professional and appointment details
- Life Space Questionnaire
- Muscle ultrasound cross sectional area of biceps brachii (3 assessments and average by 2 separate assessors)
- Muscle ultrasound cross sectional area of rectus femoris (3 assessments and average by 2 separate assessors)
- Knee to dynamometer distance (cm)
- Knee extension dynamometry at $60^0$ flexion (3 assessments and average)

- Borg rating of perceived exertion at rest
- Six minute walk test distance (m)
- Six minute walk test observations and comments
- $SpO_2$, pulse, Borg rating of perceived exertion on completion of six minute walk test
- $SpO_2$, pulse, Borg rating of perceived exertion three 3 minutes following completion of six minute walk test
- Date accelerometer started and returned
- Moderate-vigorous physical activity time (min/7days)