Statistical analysis plan, eStimCycle

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Introduction

This document describes the plan for the statistical analysis of a randomized controlled trial examining the efficacy of an intervention of early rehabilitation in critical care, known as "eStimCycle".

1.1. Abbreviations

A number of abbreviations are used in this document, as follows. In general, they are expanded fully the first time they are used.

6MWD	6-minute walk distance test
AUDIT	Alcohol Use Disorders Identification Test
BMI	body mass index
ECMO	extracorporeal membrane oxygenation
EQ-5D	EuroQOL 5 Dimensions Questionnaire
FES	functional electrical stimulation
FSS-ICU	Functional Status Score for the ICU
HADS	Hospital Anxiety and Depression Scale
HGD	hand grip dynamometer
HHD	hand-held dynamometer
ICU	intensive care unit
ICUAW	intensive care unit acquired weakness
IESr	Impact of Events Scale – Revised
INR	international normalised ratio
IQ-CODE-SF	Informant Questionnaire of Cognitive Decline in the Elderly (Short Form)
Katz ADL	Katz Index of Independence in Activities of Daily Living
Lawton IADL	Lawton Instrumental Activities of Daily Living
LOS	length of stay
MOCA	Montreal Cognitive Assessment
MRC	Medical Research Council (muscle score)
PFITS	Physical Function in Intensive Care Te**st**
SD	standard deviation
SF36V2	Short Form Heath Survey - 36 Version 2
SIRS	systemic inflammatory response syndrome
SPPB	Short Physical Performance Battery

1.2. Inclusion criteria

To be eligible participants must meet all of the following criteria:

- ≥ 18 years of age

- Individuals mechanically ventilated or using extracorporeal membrane oxygenation (ECMO)* in lieu of mechanical ventilation for > 48 hours **and** with sepsis or systemic inflammatory response syndrome (SIRS)
- Expected length of stay (LOS) in intensive care unit (ICU) ≥ 4 days (Consultant prediction)

  *Written approval must be obtained from the ICU clinician caring for a patient undergoing ECMO for >48 hours prior to enrolment in the study.

1.3. Exclusion criteria

Participants are excluded if they meet any of the following criteria:

- Individuals did not meet the safety criteria to commence intervention <72hrs
- Known primary systemic neuromuscular disease or intracranial process at admission
- Spinal cord injury
- Lower limb amputation/s
- Unable to perform study physical outcome measures premorbidly due to condition impairing mobility
- Pre-existing intellectual disability or cognitive impairment limiting the ability to accurately follow instructions
- Assessed by medical staff as not expected to survive ICU
- Pregnancy
- Body mass index (BMI) > 40 (obese)
- Presence of external fixator or superficial metal in the lower limb
- Open wounds or skin abrasions at electrode application points
- Lower limb malignancies
- Transfer from another ICU after > 2 days of consecutive mechanical ventilation
- Non-English speaking background restricting the ability to accurately and consistently follow instructions
- Incarcerated at time of ICU admission
- For cognitive assessment
  - A score of >3.3 on the IQ CODE performed by proxy at baseline.
  - A score of ≥ 10 on the AUDIT assessment at baseline
  - No fixed home address
- For muscle biopsy
  - Platelets < 40,000
  - INR >1.6

1.4. Sources of study participants

Study participants will be recruited from the intensive care units (ICUs) of four hospitals: Austin Health; Royal Brisbane Hospital; Duke University; Johns Hopkins University.

2. Design

The key feature of the design, for the purposes of this statistical analysis plan, is that it entails two groups of subjects; it is a 2-arm randomised controlled trial.

- In one arm, subjects perform functional electrical stimulation-assisted (FES-assisted) cycling, using a cycle ergometer while supine and, in many cases, sedated; the stimulation is applied to one leg only, chosen at random.
- The subjects in the other group receive standard care.

References below to "FES-assisted cycling and cycling" are to the intervention received in the treated group; the intervention is described this way because of the two legs of a subject in the intervention group: one receives FES (the FES-assisted cycle leg), and the other cycles without the assistance of FES (the cycle only leg).

It is useful to draw a distinction between the types of comparisons that will be possible.

For many of the outcomes, the measurement is taken on a whole subject (for example, functional and cognitive tests). For person-specific variables, the analysis must compare people, and will therefore be based on comparisons between the two groups of subjects in the intervention and standard care arms of the study.

For outcomes that can be measured on a specific leg (which are muscle strength and muscle mass in the quads) comparisons will be possible between the two groups, but also within the intervention group, comparing the FES-assisted cycle leg with the cycle only leg.

2.1. Trial aims

Primary Aim

To evaluate the effectiveness of functional electrical stimulation-assisted (FES-assisted) cycling and cycling compared with standard care on muscle strength and the incidence of cognitive impairment.

Secondary Aims

- To evaluate the effectiveness of FES-assisted cycling and cycling only compared with standard care on muscle mass and physical function;
- To evaluate the effect of FES-assisted cycling and cycling only compared with standard care on the prevalence of delirium;
- To evaluate the effect of FES-assisted cycling and cycling only compared with standard care on the prevalence of depression, anxiety and post-traumatic stress disorder (PTSD) in survivors of critical illness;
- To evaluate the effect of FES-assisted cycling and cycling compared with standard care on patient reported outcomes including health related quality of life physical function;
- To compare the effects of FES-assisted cycling with cycling only on muscle strength and muscle mass.

Exploratory Aims

- To establish the intracellular signalling pathways and histochemical changes responsible for muscle mass losses in septic patients;
- To investigate changes in markers of muscle protein metabolism (MPM) i.e. synthesis and breakdown across the three conditions i.e. FES assisted, cycling only and standard care

- To inform decisions about outcome measures and power calculations for future studies to describe trends of association between muscle mass, strength and physical function.

3. Outcomes (See Table 1 for time points)

3.1. Primary outcomes

The primary outcomes relate to the primary aim and are as follows.

Muscle strength will be tested using HHD testing quadriceps bilaterally using a validated protocol measured at awakening, weekly, ICU and hospital discharge (**primary time point**), 6 months and 12 months post recruitment.

A maximal isometric voluntary contraction will be assessed and the highest force (Newtons) achieved over five seconds will be recorded, three times. The force will then be multiplied by the leg length of individual participants to achieve a measure of maximal isometric torque measured in Newton meters (Nm). The highest of the three tests, will be used for analyses and will be reported in Nm. If a participant is unable to complete the test due to muscle weakness i.e. <3/5 for knee extension on MRC testing they will be scored 0; if they do not complete the test due to other reasons, the data will be considered missing.

In both the intervention and usual care arm, both legs (FES-assisted and "cycle only") will be recorded. This means the FES-assisted and "cycle only" legs in the intervention arm, and both legs in the usual care arm.

We chose to measure muscle strength at hospital discharge as our primary outcome because it was temporally related to the intervention and our collective experience in the measurement of outcomes in critical illness is that muscle strength is meaningful to the intervention of muscle stimulation and is correlated with functional outcomes (r=0.49) [1].

Cognitive impairment: The battery of validated, standardised tests (executive function, language, memory, verbal reasoning/concept formation and attention) will be performed at 6 and 12 months (6 months is the primary end point), with impairment defined in prior ICU trials having either:

- one cognitive test within the battery with a score of more than 2 standard deviations (SDs) below norms, OR
- at least 2 tests with a score equal to or more than 1.5 SDs below norms.

Six months was chosen to compare with other international data and is a valid time point for measurement of cognitive impairments.

3.2. Secondary outcomes

The secondary outcomes relate to the secondary aims and are as follows.

Muscle mass and quality

The muscle mass is measured by cross-sectional area and quality using the echointensity of the muscle from the ultrasonography of the Rectus Femoris.

Hand-grip dynamometer (HGD) grip strength

Three consecutive efforts are made. Maximal force is generated over 6 seconds. All three efforts are recorded and reported in kilograms (kg). The highest value of the three tests will be used in analyses. If a participant is unable to complete the test due to muscle weakness, they will be scored 0. If the participant can't perform the test for any reason other than weakness the data is considered missing.

Medical Research Council (MRC) muscle score

6 muscles bilaterally (3 Upper limb, 3 lower limb each side, hence 12 altogether) each tested from 0 (no contraction – 5 (full strength) presented as a sum score out of 60. A score of less than 48 out of 60 is a clinical diagnosis of ICU acquired weakness (ICUAW).

If a participant is unable to complete an element of the test e.g. elbow flexion due to positioning of an invasive device, they will be assigned the average score of the same limb.

Physical Function in Intensive Care Test – scored (PFITs)

The PFIT-s is a battery of tests used to measure endurance, strength, cardiovascular capacity and functional level. The task performed are the level of assistance from sit to stand; step cadence (steps/minute) and muscle strength. It is scored on a continuous scale of 0 (worst)-10 (best).

If up to two of the tasks are not performed due to reasons other than weakness, the average score of the remaining tasks will be attributed to the tasks not able to be tested and used to score the PFIT-s.

Functional Status Score for the ICU (FSS-ICU)

FSS-ICU measures 5 functional tasks each measured using an 8-point ordinal scale ranging from 0 (unable to perform) to 7 (complete independence). The total ordinal score ranges from 0-35 with higher scores indicating better physical functioning.

Short Physical Performance Battery (SPPB)

The SPPB is a group of measures that combines the results of gait speed, chair stand and balance tests. The measure is used as a predictive tool for disability and in the monitoring of function in older people. The test is scored on ordinal scale from 0 (worst)-12 (best) presented as a sum score.

Six Minute Walk Distance test (6MWD)

On each occasion when the 6MWT is performed according to ATS guidelines, participants complete one test and the distance in metres is recorded. One test is deemed sufficient in this patient population as there is small mean difference (meters) and range (95% CI) between the two walk tests at hospital discharge 2.2 meters (-2.7-6.1) and 6 months 3.8 meters (-11.6-3.8)[1]

Hospital Anxiety and Depression Scale (HADS)

The 14-item Hospital Anxiety and Depression Scale (HADS) is used to screen for anxiety and depression symptoms. When at least 50% of the items (7 out of 14) are recorded, the scale will be calculated as the average of the available items; otherwise, the scale will be regarded as missing [2].

Impact of Events Scale – Revised (IESr)

IESr is a self-reported questionnaire designed to measure the subjective distress caused by traumatic events. It consists of 22 questions (Intrusion: 7; Avoidance: 8; Hyperarousal: 7). Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The total score is calculated as the average of the 22 items. Avoidance is not scored if there is >2 missing items; Intrusion is not scored if >2 missing items and Hyperarousal is not scored if >1 missing item. The Total score is not calculated if there are > 5 missing items. IESr average score threshold is ≥ 1.6 to screen for PTSD in survivors, Bienvenu (2013). Since there are 22 items, an average of ≥ 1.6 corresponds to a total of ≥ 36.

SF36V2

SF-36 V2 is a generic health-related quality of life instrument consisting of 36 questions in eight domains

Scores range from 0 to 100 for each of the 8 subscales, and can be scored using standardized values (average of 50, standard deviation of 10) which are compared to norm based scores.

EQ5D

EQ-5D consists of 6 questions (Mobility: 1, Self-Care: 1, Usual Activities: 1, Pain/discomfort: 1, Anxiety/depression: 1, Health State - Visual Analog Scale: 1)

- 5 levels of severity: no problems, slight problems, moderate problems, severe problems, extreme problems.

The visual analog scale ranges from 0 to 100 with higher scores reflecting better perceived current health-related quality of life state.

KATZ Index of Activities of Daily Living (ADLs)

The Katz ADL is an instrument used to measure a patient's ability to independently perform basic activities of daily living. The index ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence and feeding. A self-report score of yes/no for independence in each of the six functions is recorded and the index reported as a sum score. A score of 6 indicates full function, 4 indicates moderate impairment and 2 or less indicates severe functional impairment. These data are collected via proxy on recruitment to the study.

Lawton Instrumental Activities of Daily Living (IADL) Scale

The IADL scale is a self-reported instrument used to assess independence in complex activities of daily living, on a numerical scale. The skills are considered more complex than activities of daily living as measured by the Katz Index of ADLs. There are eight domains of function, scored according to the highest level of functioning in each category (ability to use telephone; shopping; food preparation; housekeeping; laundry; mode of transport; medication management; handling finances). A sum score ranges from 0 (low function, dependent) to 8 (high function, independent). These data are collected via proxy on recruitment to the study.

Muscle biopsy (To be reported in separate paper)

For participants enrolled at Austin Health and Johns Hopkins, muscle biopsy biospecimens were obtained for future analysis. A small subgroup of patients will be invited to provide samples of muscle at ICU admission and discharge.

All-cause mortality

Mortality will be recorded up until one-year post recruitment; where patients withdraw or become lost to follow-up the last known date of contact will be recorded.

4. Measurement schedule

The following table shows the outcomes that will be measured, and the time-points at which they will be recorded.

Table 1: Planned outcome time point measures (note volitional tests will most often not be able to be performed at the baseline time point.)

Outcome	Pre-randomization	Initial measurement	ICU DC	Hospital DC	6 Months	12 Months
Primary Outcome						
Muscle strength: Hand held dynamometry – Quads			X	**X**		
Cognitive impairment: Cognitive Battery					**X**	X
Secondary Outcomes						
Muscle Mass: Ultrasound	X			X		
Muscle strength: Grip strength & MRC sum score			X (MRC Only)	X	X	X
Physical function						
PFITs			X			
FSS-ICU			X			
SPPB					X	X
6MWD				X	X	X
Psychological dysfunction HADS/ IESr					X	X
Patient reported outcomes						
SF36V2					X	X
EQ5D					X	X
KATZ ADL	X				X	X

Lawton IADL	X				X	X
Exploratory Aims						
Biopsy	X		X			

5. Analysis

5.1. Analysis principles and general considerations

Mortality will occur throughout the trial, particularly during the ICU stay. Based on data from prior studies, for the primary and secondary outcomes, we assumed that the intervention does not affect mortality, and that therefore a "survivors only" analysis is valid. In other respects, analyses will be conducted with subjects retained in their original assigned groups and stratified by site. This means that analyses will be modified intention to treat; no missing values due to mortality will be imputed, and deaths prior to an analysis time point will be omitted from analysis at that time point.

The one exception to this is all-cause mortality, which will be on a strict intention to treat basis, with all patients included in the analysis.

Analyses will be unadjusted for the effects of other covariates except where applicable (as described below). Where there are missing observations, the number of observations used in the analysis will be reported. No adjustment for multiple testing was planned; therefore, the secondary analyses should be considered exploratory.

The differences in baseline values between the two groups at recruitment will be described in a standard way, with percentages for categorical variables and means and standard deviations for continuous variables. No hypothesis tests will be carried out for these comparisons.

Estimates and 95% confidence intervals will be reported for treatment effects, comparing the two study groups, for all relevant outcomes. This will also be done for the possible comparisons between the FES-assisted and "cycle only" legs in the intervention arm.

The patient cohort studied is such that they may not be conscious at recruitment; subjects' next of kin will provide informed consent at that time, and the consent of the subjects themselves will be obtained when they regain consciousness and able to consent. This raises an important issue for analysis. Measurements that require subjects to be conscious and able to co-operate, including performance-based tests, will not be available at recruitment.

However, intervention will commence immediately following recruitment, and it is plausible that will be a treatment benefit between recruitment and awakening. Therefore, it is not suitable to use "change from awakening" as an outcome variable, since some of the treatment benefit may be lost.

For this reason, variables that cannot be measured on all subjects at recruitment, due to sedation and other factors, will not use a change score as an outcome. This is almost all variables. The randomisation will balance the groups, on average, so an analysis of the end-point measure will be valid. However, a more precise treatment effect may be obtained by adjusting for baseline covariates that are plausibly related to the outcome. Here the trial will

have one such covariate available, namely, muscle mass. Co-morbidity is also likely to explain variation in continuous outcomes. Therefore, adjustment for baseline muscle mass, Charlston Co-morbidity Index and the Functional co-morbidity index will be carried out for any of the outcomes relating to muscle strength.

For muscle mass itself, the same approach will be used.

Similarly, for continuous measures relating to physical function (SF36, 6MWD), it is proposed the key analyses will use the measurements at the relevant end-point, adjusted for baseline muscle mass and the two co-morbidity indices.

For cognitive and psychological outcomes that are binary, efficiency gains do not occur in the same way and therefore for these outcomes, no adjustment for baseline variables will be made.

5.2. Analysis of primary outcomes

The **quadriceps HHD muscle strengt**h at hospital discharge, 6-month follow-up and 12-month follow-up will be compared between the three "treatments", using a mixed model, with "subject" as a random effect, "treatment" (FES/cycle only/standard care) as a fixed effect and the two co-morbidity indices and baseline muscle mass as covariates. Pairwise comparisons will be analysed, for

- the FES-assisted leg compared to the average of the right and left leg in the standard care arm;
- the cycle only leg in the intervention arm compared to the average of the right and left leg in the standard care arm;
- the FES-assisted leg compared to the passive leg, in the intervention arm.

Because of the progression of mortality over the period of the analysis of the primary outcome, and the plan to do a survivors only analysis (no imputation of muscle strength for patients who have died) these analyses will be done separately for each time point. The primary time point, as noted above, is hospital discharge. Further, the primary comparison is the first of the three above, namely, FES-assisted leg versus the average of the right and left leg in the standard care arm.

The outcome for **cognitive impairment** is binary. It is assessed at the 6-month and 12-month time points (6-month is the primary endpoint). The analysis will be a difference of proportions, comparing the two groups of subjects, with the P-value obtained from Fisher's exact test and the estimate and 95% confidence interval for the difference of proportions obtained from the standard normal approximation.

5.3. Analysis of secondary outcomes

Muscle mass at hospital discharge, will be compared between the three "treatments", using a mixed model, with "subject" as a random effect, "treatment" (FES/passive/standard care) as a fixed effect and the two co-morbidity indices and baseline muscle mass as a covariate. Pairwise comparisons will be analysed, for

- the FES-assisted leg compared to the average of the right and left leg in the standard care arm;
- the cycle only leg in the intervention arm compared to the average of the right and left leg in the standard care arm;

- the FES-assisted leg compared to the cycle only leg, in the intervention arm.

MRC score muscle strength for the lower limb at hospital discharge, 6-month follow-up and 12-month follow-up will be compared between the three "treatments", using a mixed model, with "subject" as a random effect, "treatment" (FES/cycle only/standard care) as a fixed effect, and the two co-morbidity indices and baseline muscle mass as a covariate. Pairwise comparisons will be analysed, for

- the FES-assisted leg compared to the average of the right and left leg in the standard care arm;
- the cycle only leg in the intervention arm compared to the average of the right and left leg in the standard care arm;
- the FES-assisted leg compared to the passive leg, in the intervention arm.

MRC sum score muscle strength at hospital discharge, 6-month follow-up and 12-month follow-up will be compared between the two groups, intervention and standard care, using linear model with treatment (intervention/standard care) as a categorical explanatory variable, and the two co-morbidity indices and baseline muscle mass as a covariate.

The MRC score is also used to define ICU acquired weakness (ICUAW), with a score of less than 48/60 indicating ICUAW. ICUAW will be assessed at hospital discharge, 6-month follow-up and 12-month follow-up. The analysis will be a difference of proportions, comparing the two groups of subjects, with the P-value obtained from Fisher's exact test and the estimate and 95% confidence interval for the difference of proportions obtained from the standard normal approximation.

SPPB is a performance-based measures of physical function and will be evaluated at ICU discharge, 6-month follow-up and 12-month follow-up. For each time-point separately, SPPB will be compared between the two groups, intervention and standard care, using a linear model with treatment (intervention/standard care) as a categorical explanatory variable, and the two co-morbidity indices and baseline muscle mass as a covariate.

6MWD is also a performance-based measure of physical function. It will be measured at hospital discharge, 6 months and 12 months. For each time-point separately, the 6MWD will be compared between the two groups, intervention and standard care, using a linear model with treatment (intervention/standard care) as a categorical explanatory variable, and the two co-morbidity indices and baseline muscle mass as a covariates.

HADS, IES-r, SF36V2, and EQ5D are all patient reported outcomes of health-related quality of life, psychological or cognitive function, and will be measured at 6 and 12 months follow-up. At each of these time points, these variables will be compared between the two groups, intervention and standard care, using a linear model with treatment (intervention/standard care) as a categorical explanatory variable. These are simple two sample t-tests. **Katz ADL** and **Lawton IADL** will be measured at enrolment, and 6 and 12 months follow-up. At 6 months and 12 months separately, these variables will be compared between the two groups, intervention and standard care, using a linear model with treatment (intervention/standard care) as a categorical explanatory variable, and the baseline value of the measure as a covariate.

5.4. Survival analysis

Analysis of all-cause mortality will include comparisons between the two study groups using Kaplan-Meier curves and the log-rank test. Median survival will be estimated and compared using a 95% confidence interval. The estimate of the hazard ratio (intervention versus usual care) for survival, with 95% confidence interval and P-value, will be obtained from Cox's proportional hazards model.

5.5. Per Protocol Analysis

After the blinded intention to treat analysis is completed, the statistician will be advised of the adhering subjects in the intervention group, and an analysis will be carried out of the compliant group versus the control group (omitting the non-adhering subjects in the intervention group). "Adhering" will be defined as completing three or more cycling sessions of 45 minutes or more during their ICU admission. The outcomes to be analysed are strength, 6MWD and presence of cognitive impairment.

5.6. Dealing with missing values

It is expected that there will be missing data arising from a variety of sources. The description of the measures (above) deals with the cases where a missing observation may arise from partial responses on a scale, where a subject has provided responses for some but not all items.

In addition, there will be data missing because a study participant does not provide data at follow-up times.

The reasons for this could be withdrawal, loss to follow-up, or death.

It is also possible that, at a follow-up time, a subject may provide some measures but not others; for example, they may provide self-reported data (HADS, etc.) but be unwilling to provide the 6MWD test.

Up until hospital discharge, loss to follow-up will be predominantly due to death, or study withdrawal.

For most analyses, multiple imputation will be used, to enable the inclusion of all subjects alive at the time-point of the analysis. This imputation will be carried out for survivors only. It is described below.

Multiple imputation will be used to impute missing data that is assumed to be "missing at random" according to the formal definition: the probability of being missing depends on other variables and not on the value of the missing observation.

The approach taken to this will be that the multiple imputation will be done separately for:

1. Data up to and including ICU discharge, for analyses at ICU discharge;
2. Data up to and including hospital discharge, for all analyses relating to the in- hospital period;
3. Data for the 6-month follow-up, for analyses at that time point;
4. Data for the 12-month follow-up, for analyses at that time point

5.7. Sensitivity analyses

The primary outcomes analyses proposed above are "survivors only" analyses, and therefore modified intention-to-treat. To address any potential issue arising from the omission of deaths, an analysis will be carried out by constructing a composite outcome as follows, using all subjects, on a strict intention to treat basis.

At hospital discharge, the average of the strength in both legs will be calculated, for all subjects in whom the measurements are available.

For subjects alive at hospital discharge but without muscle strength data, multiple imputation will be used.

For deaths, a value lower than the minimum average muscle strength will be assigned, thus making this a composite outcome.

This composite outcome will then be analysed using a Mann-Whitney test; since this is distribution free and relies only on the ranks of the data, it makes no assumption about the meaning of the value assigned for the deaths, other than that they are worse than any of the living subjects.

For cognitive impairment at 6 months, the same approach will be used; in this case, there will be three levels of the composite outcome, which will be considered ordinal for the purposes of analysis: no impairment, impairment, and death.

5.8. Trajectory analyses (To be reported in separate paper)

For the primary outcome of leg muscle strength, we will compare trajectories in all patients with data at the initial time point (i.e. awakening). We will examine the trajectories of muscle strength across the time points ICU discharge, hospital discharge, 6 months, and 12 months, using a linear model with main effects for time as a categorical variable and treatment, and an interaction term for time and treatment. The linear model will be fit with a working independence assumption and standard errors generated via non-parametric bootstrap procedure where patients are sampled with replacement to account for the within-subject clustering over time. Multiple imputation will be used for missing data, apart from deaths; data will be used or imputed for patients while alive, but no imputation will be carried out for time points after a subject has died.

For the secondary outcome of 6 MWD, the same approach will be used, for the time points hospital discharge, 6 months and 12 months.

References

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