Non-CTIMP Study Protocol

Anaemia & functional capacity, fatigue, daily activity, sleep and Circadian Rhythm Disruption among critical illness survivors

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Amendment classification and number:	**Summary of change(s)**
A	The recruitment window had been prolonged from 7 to any time since ICU to hospital discharge.
C	For patients who find the exercise test burdensome, allow participation in all other aspects whilst omitting the exercise test.
C	Questionnaires (VAS-F and BI) on the day of the exercise test will be distributed only if more than 48 hours passed since recruitment
A	Study inclusion criteria have been broadened to cover those after level 2 care (at least one organ support) and/or HDU patients compared to the previous level 3 care only as well as time treated in the ICU or/and HDU reduced to over 24 hours
A	Inclusion criteria for group one were changed from at least 72 hours of mechanical ventilation to over 24 hours
A	The fourth patient group was added formed of patients who have not been mechanically ventilated while receiving ICU or/and HDU care
A	Two exclusion criteria regarding pre-existing major physical impairments affecting activities of daily living and clinical escalation pathways, which exclude patient escalation to level 3 care, were added.
A	Additional patient data regarding a hospital readmission rate during the first 3 months after discharge that can be collected from the electronic medical records alone, in retrospect, have been proposed.
C	The second recruiting site as represented by the Western General Hospital Edinburgh was added.

CONTENTS

LIST OF ABBREVIATIONS

Insert abbreviations as required

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
DO_2	Oxygen Delivery
ADL	Activity of Daily Living
APACHE	Acute Physiologic Assessment and Chronic Health Evaluation
ASA	American Society of Anaesthesiologists Physical Status Classification
AT	Anaerobic Threshold
AWI	Adults with Incapacity
CI	Chief Investigator
CO	Cardiac Output
CPET	Cardiopulmonary Exercise Test
ALI	Acute Lung Injury
CRF	Case Report Form
GCP	Good Clinical Practice
RBC	Red Blood Cells
Hb	Blood haemoglobin concentration
HDU	High Dependency Unit
HQL	Health Related Quality of Life
HRG	Healthcare Resource Group
Ht	Haematocrit
ICH	International Conference on Harmonisation
ICH	International Conference on Harmonisation
ICD	Ischemic Cardiovascular Disease
ICU-AW	Intensive Care Unit - Acquired Weakness
IL	Interleukin

ISD	Information Services Division (Scotland)
MODS	Multi Organ Dysfunction Syndrome
MRC	Medical Research Council Score
MV	Mechanical Ventilation
NHS	National Health Service
PI	Principal Investigator
PICS	Post Intensive Care Syndrome
PSSRU	Personal Social Services Research Unit
QA	Quality Assurance
SD	Standard Deviation
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
VWU	Ventilator Weaning Unit
VAS-F	Visual Analogue Scale - Fatigue
VO_2	Oxygen Consumption
WR	Work Rate
ARDS	Acute Respiratory Distress Syndrome
SARS	Sever Acute Respiratory Syndrome

1 BACKGROUND

According to the UK Intensive Care National Audit and Research Centre [ICNARC] in 2017-18 there were 175,700 intensive care unit (ICU) admissions in England, Wales and Northern Ireland that experienced a 19.5% crude hospital mortality. The length of in-hospital stay following critical care unit discharge was 15.3 (SD 22.6) days. During the same period, according to Scottish Intensive Care Society Audit Group data (2019), 46,166 patients required ICU care and/or combined ICU/high dependency unit (HDU) treatment in Scotland with an overall in-hospital death rate of 18%.

Critical care survivors are a distinct patient population who experience many ongoing health-related issues, difficulties in maintaining activities of daily life activities (ADL), a significantly decreased quality of life and higher odds of mortality over a long period following ICU discharge (Hashem et al. 2016); (Herridge et al. 2011); (Ramaiah and Kirk-Bayley 2011); (Dowdy et al. 2005); (Desai, Law, and Needham 2011). The extent of the post-critical illness sequelae depends not only on inherent individual factors but on disease severity that is reflected in the number of organs/systems that should be externally supported, either mechanically or pharmacologically. On this basis, patients in the advanced care units are extremely heterogeneous and might be conventionally separated in relation to the number of failed body systems. On a large scale, such a separator is considered to be mechanical lung ventilation and its duration. Moreover, the extent of the disease-related organ damage is proportionate to the financial pressure on both individual and healthcare levels.

1.1 ICU Acquired Weakness

The majority of critical illness survivors who received mechanical ventilation for over 48 hours experience difficulties in three domains: physical, psychological and social which are aggregated under the term “post-intensive care syndrome” (PICS), which affects their wellbeing for a long period afterwards (Van Der Schaaf et al. 2009); (Hopkins et al. 2017). Muscle weakness attributable to the critical illness episode is known as ICU acquired weakness (ICU-AW) which constitutes a part of PICS. It is estimated that during critical illness, patients lose approximately 2-3% of muscle mass per day, which results in impaired muscle strength, conductivity, quality, and quantity of myofiber. This can persist for a protracted period (Puthucheary et al. 2015); (Parry et al. 2015). The incidence of ICU-AW varies widely between studies and different ICU populations, ranging from 9 to 86% with a mean 40% rate (Appleton, Kinsella, and Quasim 2015). Typically, diagnosis of ICU-AW is based on the Medical Research Council (MRC) score, which assesses 3 muscle groups in each of the upper and lower limbs(De Jonghe et al. 2002); (Hough, Lieu, and Caldwell 2011). Development of ICU-AW has both strong and positive associations with illness severity (APACHE II score ≥12), use of neuromuscular blocking agents, aminoglycoside antibiotics class, infection-related conditions (sepsis, septic shock) and its duration, either electrolyte or glucose abnormalities and malnutrition (Yang et al. 2018). In general, greater severity and duration of critical illness are associated with a greater probability a patient will have ICU-AW after ICU discharge.

1.2 Management of ICU-AW

Unfortunately, pharmacological agents that have been tried to treat this pathology have not improved or prevented ICU-AW. A possible but controversial exception may be intensive insulin therapy, although this may be at the cost of dangerous hypoglycaemic episodes and increased mortality and is not the current standard of care. Early mobilisation-rehabilitation programs in the ICU may reduce the duration of ventilation and are thought to decrease the incidence and severity of ICU-AW; this can be applied safely to most patients (Hermans et al. 2014). However, the optimum method and intensity of providing early mobilisation, the groups that benefit most, and effects on long-term outcomes remain uncertain and unproven.

Physical rehabilitation is an integral part of strategies to promote recovery from a wide range of acute and chronic health-related conditions and has proven benefits for many conditions. As an example, O’Connor and colleagues(1989) reported that a physical rehabilitation program after acute myocardial infarction was associated with a 20% reduction in mortality. Although systematic reviews illustrate the controversies in this area (L. Anderson et al. 2016) the impact

of physical activity on cardiovascular mortality and its association with improved patient-reported quality of life are widely established in conditions such as cardiorespiratory disease.

Although biologically plausible and widely believed, the impact of physical therapy on outcomes for critical care survivors is uncertain and contradictory in different studies (B. Connolly et al. 2015). Evidence is strongest for interventions applied early during ICU care, especially regarding short-term outcomes (D. McWilliams et al. 2017); (Bemis-Dougherty and Smith 2013). In contrast, rehabilitation interventions initiated in the post ICU period seem less beneficial, and the results of published studies are inconsistent. Other options for alleviating muscle weakness include electrical muscle stimulation, but these still have to be thoroughly investigated(B. Connolly et al. 2016). Despite widespread calls from the academic and clinical community for clinicians to implement early mobilisation and physical rehabilitation in ICU, recent evidence shows that in UK's ICUs regardless of either organ support, sedation, or day of the week, patients spent approximately two-thirds of the day without engaging in any kind of physical activity. These findings were echoed in a cohort of longer-term critically ill patients in a ventilator weaning unit (VWU)(B. A. Connolly et al. 2019). The National Institute for Health and Care Excellence (NICE) guidelines(p19.,2009) state the following: "Currently, rehabilitation strategies after a period of critical illness tend to be disease-specific and provided by specialist neuroscience, cardiac services, burns or other units. For general adult critical care patients who do not fall into existing rehabilitation services, alternative rehabilitation pathways are currently poorly defined, variable, or do not currently exist". Thus, the need to understand the optimum methods of providing rehabilitation and promoting recovery in general critical illness survivors during the post-ICU period is required.

1.3 Anaemia and its current management in critical care patients

In accordance with the World Health Organization (WHO): *"Anaemia is a condition in which the number of red blood cells or the haemoglobin concentration within them is lower than normal. Haemoglobin is needed to carry oxygen and if you have too few or abnormal red blood cells or not enough haemoglobin, there will be a decreased capacity of the blood to carry oxygen to the body's tissues. This results in symptoms such as fatigue, weakness, dizziness and shortness of breath, among others. The optimal haemoglobin concentration needed to meet physiologic needs varies by age, sex, the elevation of residence, smoking habits and pregnancy status"* (available at https://www.who.int/health-topics/anaemia#tab=tab_1). Generally, this happens during and after a decrease in the circulating red blood cell volume together with haemoglobin concentration and can occur for various reasons. According to a plethora of studies, anaemia is one of the most frequent complications of critical illness and can persist in those who survive the critical phase.

In general terms, anaemia is caused by three types of abnormalities: Impaired red blood cell production; increased destruction of red blood cells; and blood loss. All the reasons listed above might be present and coincide with a critically ill individual. It has been estimated that during the course of critical illness during ICU stay haemoglobin (Hb) concentration decreases on average by 0.52 +/- 0.69 g/dL/day in non-bleeding patients, with a maximum rate during the first 3 days, then slowly but steadily afterwards (Nguyen et al. 2003). Anaemia prevalence among critically ill patients experiencing prolonged ICU stay is up to 97-100% and as a consequence, 75-97% of ICU survivors have various degrees of anaemia at ICU or hospital discharge (Walsh et al. 2006); (Shah et al. 2016); In addition, normal physiological responses to anaemia are impaired, and the body responds poorly to erythrogenesis stimulating agents, such as erythropoietin. This is probably due to bone marrow suppression mediated by an ongoing inflammatory process, including through the key regulating hepcidin pathway (Loftus et al. 2018). Nonetheless, at present, only around 19% of anaemic patients receive RBC transfusion post ICU on general wards to correct anaemia (Shah et al. 2016).

A landmark trial by Hébert et al. (1999) demonstrated that a restrictive transfusion strategy is not inferior to liberal practice. Since the publication of this trial, evidence-based medical practice has shifted toward restrictive use of blood transfusion for anaemia management, typically only transfusing red blood cells when the haemoglobin concentration is less than 70-80 g/L. However, in recent years concern has been raised that this approach may not be optimum for all patients, and a higher haemoglobin level may benefit specific patient groups such as those

with underlying cardiovascular disease (ICD) (Docherty et al. 2016), haemoglobinopathies (DeBaun et al. 2014), traumatic brain injury (TBI) (Meyfroidt et al. 2019), (Gobatto et al. 2019) and in elderly populations (Simon et al. 2017). Despite alternative pharmacological approaches to anaemia treatment such as erythropoiesis-stimulating agents and supplemental iron along with vitamin therapy, the only anaemia intervention that immediately increases blood oxygen carrying capacity by correcting anaemia is red blood cells (RBC) transfusion.

1.4 Economic impact of critical illness

According to Griffiths and colleagues (2017) in the UK, 40% of critical illness survivors were employed prior to illness, of whom 33% and 28% experienced a negative impact on employment status at 6 and 12 months, respectively. Patients may become either unemployed, take early retirement, switch to part-time work or take long-term sick leave. This affects families' financial status and security. Furthermore, a quarter of survivors require assistance in daily life activities, which were provided by family members in 80% of cases, who had to adjust their working schedules accordingly. In addition, healthcare resource utilization rises dramatically after critical illness (Szakmany et al. 2019). A study conducted by Lone and colleagues (2016) in Scotland measured the economic impact on healthcare systems of critical illness on survivors during the 5 years following hospital discharge. The study demonstrated significantly higher rates of hospital admission, especially during the first year after an index critical illness event with a 51% increase in mean costs ($25,608) per person, compared to hospitalized individuals free of ICU stay (Lone et al., 2016). Thus, the financial burden and an increased workload on healthcare workers and carers, and decreased survivors' quality of life are still major challenges in this healthcare area. Interventions that are effective in improving recovery bear the potential of economic benefits at both personal and societarian levels.

1.5 Fatigue among critical illness survivors

Fatigue is a heterogeneous and multifactorial condition without a commonly accepted definition. It can be present in apparently healthy individuals ('physiological' fatigue) as well as in diseased patients ('pathological' fatigue). Patients typically describe fatigue as a feeling of weakness, tiredness and inability to concentrate on tasks (Landmark-Høyvik et al. 2010). Interestingly, fatigue in healthy individuals might be considered a protective physiologic reaction to prolonged intense activity or stress, but is usually self-limiting and completely resolves after rest (Kluger, Krupp, and Enoka 2013). Historically, this was first described by the influential Italian physiologist Angelo Mosso (1846-1910) "*what at first sight might appear an imperfection of our body, is on the contrary one of its most marvellous perfections. The fatigue increasing more rapidly than the amount of work done saves us from the injury which lesser sensibility would involve for the organism*" (Mosso 1906). In contrast, during any pathological condition, the feeling of fatigue becomes extremely common and prominent even after rest, with exhaustion even during regular activities. In these situations, fatigue can be associated with acute illness, but persist during convalescence with the potential to become chronic. Fatigue is a prominent feature of many chronic diseases (Davis and Walsh 2010).

Two types of muscle-related fatigue have been described: 'central', which is caused by an alteration in intensity and speed of neuro-signalling from the motor cortex; and, 'peripheral' caused by disrupted metabolic processes at neuromuscular junctions and beyond within muscle cells (Taylor, Todd, and Gandevia 2006).

Fatigue is a prominent feature of anaemia. As the majority of critical illness survivors remain anaemic, potentially for prolonged periods following ICU discharge, and also experience weakness and fatigue, it is possible these important symptoms are causally interrelated. These problems may strongly influence the poor health-related quality of life reported by survivors. Quality of Life questionnaires capture domains that include both physical and psychological aspects of health that are likely to be affected by fatigue.

1.6 Assessing patients' physical status after intensive care discharge

A range of potential approaches is available to objectively assess ICU survivors' physical status after discharge from the ICU. These vary in terms of complexity, feasibility, and cost and are likely to have differing potential to discriminate between different individuals. Prior to inclusion in any randomised trial to assess whether blood transfusions may improve physical function and fatigue after ICU discharge these require evaluation.

1.7 Cardiopulmonary exercise testing

Health status correlates better with physiological measures assessed during exercise than with the same measures taken at rest (Wasserman 1997). Cardiopulmonary exercise testing (CPET) is an objective, non-invasive assessment of the integrated physiologic interaction of cardiovascular, pulmonary, and muscle systems under load. Information supplied by this method might identify the causative reasons which underlay exercise intolerance and overall functional capacity, allowing a prediction of how an individual might respond to stress, for example, undergoing major surgery.

During CPET, an array of physiological variables is obtained and the most clinically important being a maximal oxygen consumption (VO2max), oxygen consumption at anaerobic threshold (AT) and work rate (WR), which an individual can reach during incremental exercise. More to the point, the AT is a non-volitional variable, which is thought not to be affected by the patient's effort or any learning effect that makes it less biassed. There are two main approaches to assessing exercise capacity using CPET: treadmill and cycle ergometer-based tests. In both cases, the range of physiologic variables is measured continuously as the patient undertakes a pre-defined incremental exercise protocol. Measured variables include blood pressure, electrocardiogram (ECG), spirography, tissue oxygen saturation and inhaled/exhaled gas analysis. These enable a calculation of variables such as oxygen consumption (VO2) (American Thoracic and American College of Chest 2003). The main domains of CPET usage are identifying the cause of exercise limitation and as a predictive tool of unfavourable outcomes and as a method for pre, intra and post-operative management among patients with serious comorbidities before elective major surgeries (Andres Porras et al. 2017); (Older et al. 1993); (Knight. et al. 2014); (Levett et al. 2018);

1.8 CPET and measures of exercise capacity among critical illness survivors

Many studies have assessed critical care survivors' cardiorespiratory fitness, but most of these studies used a six-minute walk test (6MWT). Findings showed significantly decreased functional capacity, which improved over time but was still below population average levels. Interestingly, individuals who had experienced acute respiratory distress syndrome (ARDS) had poorer functional improvement compared with those who did not experience this complication of critical illness (Parry et al., 2019). In a study exploring ICU survivors' functional capacity before hospital discharge, patients aged 50-70yr, who had been on a ventilator for over 4 days could walk 49-372 meters on a day 6-7 after ICU discharge which was only 27% of the predicted distance (Waters et al., 2015).

Few studies have been undertaken on critical care survivors' functional capacity assessed using CPET. We found only six published studies which are summarised in Table 1 below.

Table 1. Studies which assessed critical illness survivors' functional capacity in terms of CPET

Author	Population/ comparator	Number of participants	Timing of the testing	Peak VO2 L/m, ml/kg/min, mean, range or SD, predicted (%) Work rate (watts)		VO2 at AT L/min; ml/kg/min, mean, range.	
Mackney et al,. (2019).	ALI survivors/ healthy individuals	10	42 days after hospital discharge.	**ALI survivors** 1.45 ± 0.37l/m 17.8 ml/kg/min (14.9-20.9) 71 ± 23% 90W (76-120)	**Healthy individuals** 2.46 ± 0.89l/m 31.80 ml/kg/min (26.60-41.73) 120 ± 33% 180W (135-250)	**ALI survivors** 0.78 l/m (0.69-0.94) 9.83 ml/kg/min (8.52-11.12)	**Healthy individuals** 1.20 l/m (0.98-1.73) 15.83 ml/kg/min (13.76-22.40)
Benington, S. et al., (2012).	General ICU survivors	50	24 ± 14 days after hospital discharge	**Ventilated 5-14days** 15.3 ml/kg/min Range (8.9-23.8) 60.7% (26-87)	**Ventilated for more than 14 days** 13.4 ml/kg/min Range (8-21.2) 52.7% (24-83)	**Ventilated for 5-14days** 11.7 ml/kg/min Range (8.1-16.8) 45% (37-73)	**Ventilated for more than 14 days** 9.97 ml/kg/min Range (6.4-17.7) 43.3% (21-71)
Neff, T.A. et al., (2003)	Trauma ARDS survivors	12	29.5 ± 8.7 months after hospital discharge	**ARDS survivors** 2.02±0.376 l/m 24 ± 7 ml/kg/min 77±13% Watts predicted			
Mcwilliams, D., Bennington, S. & Atkinson, D., (2016)	Gensurvivor's survivors standard care/exercise rehabilitation program	73	24 ± 13 days after hospital discharge 8-10 weeks follow-up.	**Control group** **Baseline** 13.6 (3.9) ml/kg/min56.3% (15.6) **Follow-up** 15.5 (5.4) ml/kg/min 62.5% (16.3)	**Rehabilitation group** **Baseline** 13.8 (3.7) ml/kg/min 52.3% (13.0) **Follow-up** 16.4 (4.9) 62.4% (18.4)	**Control group** **Baseline** 10.3 (3.4) ml/kg/min **Follow-up** 11.5 (3.7) ml/kg/min	**Rehabilitation group** **Baseline** 10.3 (2.5) ml/kg/min **Follow-up** 11.8 (3.4) ml/kg/min
Ong, K.C. et al., (2004)	SARS survivors	44 but only 7 of them required MV	90 days after hospital discharge	1.2±0.4 (0.6–2.2) l/min 20.3±5.1 (11.2–30.6) l/kg/min 78.6±17.0% (44.4–113.8) 95.3±30.4 Wats 80 ± 21.2% of predicted Wats			
Batterham A. M. et al,. (2014)	ICU survivors	59	Baseline, 9 and 26 weeks after hospital discharge.	Control group	Intervention group	Control group 10.4 (2.8)	Intervention group 10.4 (3.5)

Peak VO_2 – peak oxygen consumption, **VO_2 at AT** – oxygen consumption at anaerobic threshold, **SD** – standard deviation, **MV** – mechanical ventilation, **ALI** – acute lung injury, **ARDS** – acute respiratory distress syndrome, **SIRS** – sever acute respiratory syndrome.

Data from the small number of published studies suggest that critical illness survivors have significantly impaired functional capacity compared to control individuals based on CPET, but this improves over time. However, some patients have exercise limitations even years after ICU discharge. No serious adverse events have been reported during these CPET studies. The CPET method proved to be safe among this population and could be used as an objective assessment tool for different treatment approaches. However, limited studies and a small participant number are currently available. All studies mentioned above, explored exercise tolerance at least two weeks after hospital discharge, rather than at an early point following ICU discharge. More data concerning critical illness survivors' functional status and capabilities are needed to better understand the use of CPET to measure functional limitations in this population, and the impact of interventions that may improve the recovery trajectory.

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1.9 Daily activity and quality of sleep measured by wearable accelerometer device among critical illness survivors

During the past decade, there has been a growing interest in patient-centred post-critical illness outcomes. This has encouraged researchers to investigate issues and feasible solutions around early mobilization-rehabilitation, maintaining minimal sedation, and sleep quality enhancing strategies that have led to changes in critical care clinical practice (Devlin et al., 2018);(Needham et al., 2012); (Barr et al., 2013).

Wearable electronic devices supplied with various sensors, which might collect an array of data regarding temperature, the quantity of illumination, multi-axis movement, speed and many other physiological or environmental variables, have been rapidly developing and infiltrating every aspect of current society. In the healthcare system, such methods are gaining interest, particularly in the assessment of sleep patterns and daily physical activity for their simplicity and comfort compared with conventional methods. In addition, these methods have been well-validated among the general healthy population and are currently in widespread use among fitness gadgets, such as smartwatches from a range of manufacturers (de Zambotti et al., 2018). A week-long accelerometery data from over 100 000 volunteers and 20 000 of which have repeated recordings are available at the UK BioBank (https://www.ukbiobank.ac.uk/about-biobank-uk/) for a moderate fee.

In the professional healthcare area, this method is still at the validation and test stage. For instance, sleep patterns recorded by a wearable electronic accelerometery device when compared with polysomnography (PSG), which is considered the gold standard of sleep assessment, yielding promising results in terms of accuracy (Haghayegh et al., 2019). While the reliability of wearable accelerometers regarding physical activity, movement, mobility, and overall functional behaviour among critically ill patients at various clinically important points are variable but in published studies have an acceptable correlation with other activity measurements (Anderson et al., 2018); (Verceles and Hager, 2015).

Modern accelerometers can provide RAW acceleration data that widens the analytical possibilities. Most acceleration data analysis algorithms have been based on data obtained from healthy volunteers, hence raising the concern about their validity among populations with underlying diseases (Tsanas, Woodward, and Ehlers 2020), (Conley et al. 2019). Therefore, more studies are still required that will aid this method, along with developing and tailoring disease-specific analytic algorithms, including validation against other mobility scales.

Key advantages of the accelerometery are unobtrusiveness compared to other methods used to access physical activity, like direct observation or video monitoring and the possibility to collect activity data for a long period. Further, recorded data can describe both physical activities and sleep patterns during everyday living by applying custom analytical approaches. The development in data science enabled the detection of activity of daily living, solely from the accelerometer recordings. These make this method relevant to use in patients recovering from critical illness and have the potential to detect a difference in physical recovery trajectories between patients subjected to interventions aimed at improving functional capacity, either directly or indirectly, such as anaemia treatment with blood transfusion.

2 ABC Post ICU Trial

The UK's large multicenter ABC post-ICU clinical trial will explore the impact of the post ICU blood transfusion strategy on clinical outcomes among anaemic ICU survivors. The main aim of this trial is to determine whether a higher blood haemoglobin level achieved with RBC transfusion in the post ICU setting is beneficial in terms of symptoms of fatigue, functional status, activities of daily living, and overall quality of life compared to 'usual care' restrictive transfusion practice.

Trial's Inclusion criteria:

- Patient who required level 3 ICU care at any time point during the current hospital admission (defined as advanced respiratory support and/or at least two organ support)
- Patient considered ready for discharge from the ICU by the caring clinical team
- Hb≤94g/L when ready for ICU discharge or during the first seven days following the decision by the treating clinician that the patient is **fit for** ICU discharge
- Age ≥16 years.
- Consent provided (by a participant or in accordance with appropriate mental capacity legislation for the site)

Exclusion criteria:

- Contraindication or objection to RBC transfusion
- Active bleeding when screened
- Primary neurological ICU admission diagnosis
- Patients discharged from the ICU following cardiac surgery
- Currently receiving or planned to receive end-of-life care
- Not expected by the clinical team to survive to hospital discharge.
- Patient with a proven chronic haematological disease that requires regular RBC transfusion to treat anaemia
- Patient with dialysis-dependent chronic renal failure prior to ICU admission
- Patient receiving regular erythropoietin (or erythropoiesis-stimulating agents) treatment for anaemia prior to ICU admission.
- Unable to obtain consent (from a patient or in accordance with appropriate mental capacity legislation for the site)

All eligible participants will be subject to computer-based randomisation and centre block allocation with a 1:1 ratio into a comparator and intervention groups. It is assumed that the only difference between groups will be in-hospital anaemia management. Patients in the comparator group will be treated according to current NICE guidance (see: www.nice.org.uk/guidance/ng24/chapter/Recommendations#red-blood-cells-2) which recommends haemoglobin concentration less than 70g/L as a blood transfusion trigger and a target haemoglobin concentration between 70-90g/L while patients in the intervention group will have higher blood transfusion trigger and target concentration less than 100g/L and 100-120g/L, respectively. It ought to be remarked that patients in the intervention group will at least receive a transfusion of one RBC unit following randomisation.

The main ABC post-ICU trial does not include detailed physiological measures of functional capacity, such as CPET. In the UK, only two published randomised control trials utilised the CPET as an outcome measure among ICU survivors. Studies were conducted by Mc. Williams and colleagues (2016) and Batterham et al,. (2014). The former found no statistically significant impact from specialist physical rehabilitation on CPET measures among ICU survivors compared to regular practice, while the latter revealed minor change at the anaerobic threshold in favour of the exercise program. However, in the ABC post-ICU trial, the intervention group will have a higher oxygen-carrying capacity as a result of RBC transfusion, which could increase exercise capacity that possibly could be detected by the CPET. This would be consistent with the work of Gledhill and colleagues (1982), (1999) who showed that VO2max increases by approximately 1% for each 3 g/L increase in HB concentration among healthy athletes. This is known to improve the endurance and performance of athletes but is poorly studied during illness and among diseased individuals (Brien and Simon, 1987).

In a sub-study in one site (Edinburgh Royal Infirmary), we propose to study the differences in CPET and subjective fatigue measurement by self-reported Visual Analogue Scale Fatigue (VAS-F) between the randomisation groups in the ABC post-ICU study. Ideally, we wish to study differences between the groups when the differences in haemoglobin concentration, and therefore oxygen-carrying capacity, are greatest. This is likely to be within the first 2-3 weeks post-randomisation, which is likely to be before hospital discharge in most patients.

3 STUDY OBJECTIVES

We plan a feasibility exploratory study among survivors of critical illness to investigate whether CPET and wearable accelerometry can be used during early post-intensive care recovery.

We aim to explore the relationship between in-hospital factors, anaemia management strategy, and critical illness survivors' functional capacity, their activity of daily living, fatigue, and quality of sleep by recruiting a cohort of patients participating in a randomised trial of two strategies for managing anaemia following ICU discharge (the ABC post ICU study).

As further comparative cohorts, and to gain an understanding of functional capacity following an ICU admission, we will collect functional data on two additional cohorts: first, patients who received 24 hours or more of mechanical ventilation in the ICU, were discharged alive, but were not eligible for the ABC post ICU study due to lack of anaemia; second, patients who required level 2 care (HDU care) for at least 24 hours (no mechanical ventilation)

3.1 OBJECTIVES

- To provide objective figures regarding the functional capacity of critical illness survivors close to the point of hospital discharge.
    - Cardiopulmonary exercise test (cycle-ergometer based)
- To measure patient-reported levels of fatigue during the immediate post ICU discharge period
    - Visual Analogue Scale – Fatigue (VAS-F)
- To measure patient-reported performance in the daily living activities
    - Barthel Index (BI)
- To access day (daytime activity) and night movement (sleep patterns) of intensive care survivors for two months since enrollment
    - Wearable wrist-worn accelerometer (Geneactiv device)
- To explore the relationship between these variables and anaemia status following ICU discharge
- To compare several different cohorts of patients discharged from critical care in terms of:
    - Fatigue levels (VAS-F)
    - Activity of daily living (BI)
    - Physical activity and quality of sleep (accelerometery)
    - Cardiopulmonary exercise capacity (CPET)

3.2 ENDPOINTS

3.2.1 Feasibility endpoints

- Proportion of patients approached who agree to participate in the sub-study
- Proportion of patients who agree to take part, who are able to attempt the CPET test
- Proportion of patients who agree to take part and completed an average duration of useable accelerometer recordings
- Safety and adverse events related to the CPET and wrist actigraphy device

3.2.2 Clinical endpoints

3.2.2.1 Primary endpoints

Derived from CPET

- Peak Oxygen uptake ($VO_{2\ peak}$) (ml min^{-1} and ml kg^{-1} min^{-1})

- Oxygen consumption at Anaerobic Threshold (AT) (ml min^{-1} and ml kg^{-1} min^{-1})
- Peak work rate (WRpeak) (W)

Derived from Sleep-relatedarable actigraphy

- Sleep related variaan indicatduration,
  - movement/non-movement as an indicator of sleep efficiency
  - waking episodes
- Daily activity-related variables
  - Free-living physical activity (minutes/day)
  - Light physical activity
  - Moderate physical activity
  - Vigorous physical activity
  - Sedentary behaviour time

Derived from self-reported VAS-Fatigue and Barthel Index scales

- Subjective level of experienced fatigue
- Activity of daily living score

3.2.2.2 Secondary endpoints

- The effect of haemoglobin concentration on daily activity, sleep quality, cardiopulmonary performance and feeling of fatigue
- Causes of exercise limitation among critical illness survivors
- Possible links between ICU related factors and patient's cardiopulmonary exercise capacity, fatigue, quality of sleep and daily activity
- Possible associations between both exercise capacity (peak oxygen consumption) and daily physical activity (step count, activity counts per day, time spent in activity) with a hospital readmission rate

4 STUDY DESIGN

A prospective exploratory single-centre study, conducted in conjunction with a large multi-centre randomised controlled trial.

All eligible patients successfully discharged alive from the general ICU/HDU within the Edinburgh Royal Infirmary and Western General Hospital will be approached at the post-ICU/HDU wards and asked for consent to take part in the study.

4.1 Groups

We plan to recruit four different cohorts of patients:

Group one (feasibility group): 'ICU survivors'
These patients should have received level 3 care and ventilatory support for more than 24 hours in the ICU, and should not be involved in the ABC post-ICU trial. Patients who have contraindications for blood transfusion or rejected a blood transfusion if indicated might be included. Patients already involved in the other studies can be co-enrolled if the principal investigator agrees.

Group two: 'Anaemic ICU survivors – usual care (restrictive) transfusion strategy'
These patients will have consented to participate in the ABC-post ICU trial, and randomised to the restrictive strategy (transfused at a lower haemoglobin threshold).

Group three: 'Anaemic ICU survivors – liberal transfusion strategy
These patients will have consented to participate in the ABC-post ICU trial, and randomised to the liberal strategy (transfused at a higher haemoglobin threshold).

Group four: Patients who required high dependency care (Level 2 care) in the critical care unit
Participants in this group should have been treated for at least 24 hours at either ICU or HDU level, but required only level 2 care (no mechanical ventilation in the ICU or HDU; requirement for only single organ support).

4.2 Overview of proposed assessments and measurements.

Following the enrolment on the same day, all participants will be asked to complete short self-reported questionnaires about their ability to undertake activities of daily living (Barthel Index) and self-reported feelings of fatigue (VAS-F scale). Later, close to the point of hospital discharge or on the day of the cardiopulmonary test both questionnaires will be administered one more time.

In addition, on the day of enrolment, all participants will be asked to put on and wear an accelerometer device on their non-dominant wrist for up to 2 months, which is the usual time when the GENEActive accelerometer requires to be charged. Participants are encouraged to wear it for as long as possible, but taking it off is not prohibited. In the unlikely event that patients experience hypersensitivity or allergy to the device strap, they will be advised to stop wearing the strap and seek medical help by contacting medical services (either through their GP, emergency department or ambulance service).

Finally, for those participants who agreed to undergo the cardiopulmonary exercise test (CPET), the test will be arranged, which might happen in the interval of 5 to 20 days post ICU discharge. The CPET will take place in the hospital cardiopulmonary exercise testing laboratory and comprises a maximal, symptom-limited incremental exertion test on a cycle ergometer. All tests will be carried out according to an incremental protocol, where the increment rate of pedal resistance is calculated individually, allowing to achieve maximal exertion within 8-12 minutes, which has been shown to elicit optimal results. For more details regarding the cardiopulmonary exercise test, please see the appendix. Despite applied measures to increase the CPET completion rate among participants such as at the screening and enrollment stages, excluding patients with orthopaedic/neurologic pathology along with those who have contraindications to be tested and close collaboration with the cardiopulmonary exercise testing team, respectively, some participants might not be able to undertake or complete the test. These could be due to various individual or organizational reasons. In such cases, we will try to reschedule the exercise test and regardless of the presence or absence of the CPET result, participants will not be subjected to exclusion from the study.

Schematically the study flow is illustrated in figure 1 below.

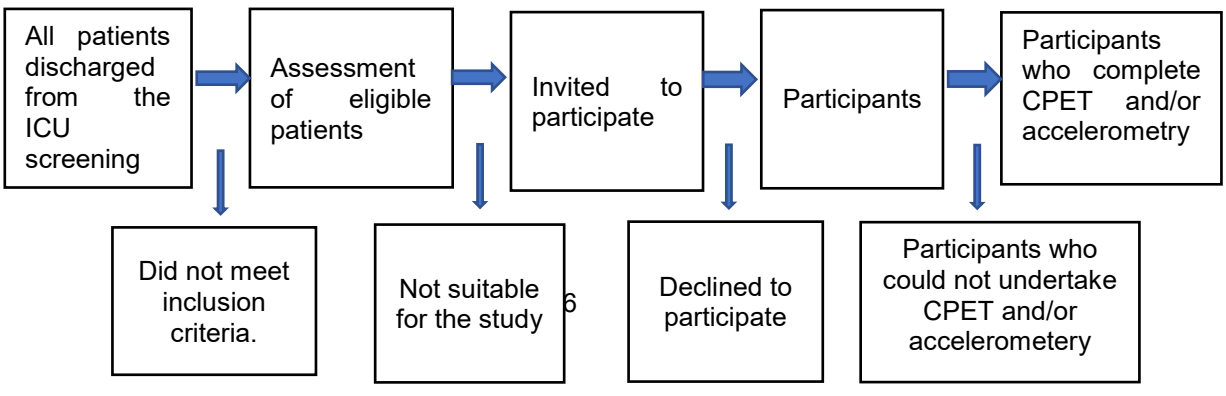

Figure 1. Study flow

5 STUDY POPULATION

Adult patients treated for at least 24 hours in the critical care unit within the Royal Infirmary Edinburgh or Western General Hospital and successfully discharged are potentially eligible for the study.

5.1 NUMBER OF PARTICIPANTS

This is a feasibility study. Target recruitment was set at 40 subjects, divided into four groups. The aim will be to recruit 10 patients to each of the patient groups. If recruitment to some groups is slow or unlikely to reach the target of 10 patients, we will increase recruitment to the other groups to achieve a total sample size of 40 patients, given the feasibility design.

5.2 INCLUSION CRITERIA (All groups)

- Patient older than 16 years.
- Patient who required either level 2 or 3 ICU care at any time point during the current hospital admission (defined as requiring support for a single failing organ system and advanced respiratory support and/or at least two organ support, respectively)
- Patients who required either level 2 or 3 care for at least 24 hours
- Patient with the mental capacity to give consent for the study

Group one:

- Critical illness survivors who have been on mechanical ventilation for more than 24 hours
- Not involved in the post-ICU ABC trial and might have a contraindication or objection to blood transfusion

Group two:

- Patient enrolled in the restrictive transfusion strategy group of ABC post ICU trial (Haemoglobin concentration at ICU discharge of >94g/L)

Group three:

- Patient enrolled in the liberal transfusion strategy group of the ABC post ICU study (Haemoglobin concentration at ICU discharge of >94g/L)

Group four

- Critical illness survivors who have not been mechanically ventilated in the ICU or HDU, and received level 2/HDU care for at least 24 hours

5.3 EXCLUSION CRITERIA (All groups)

- Active bleeding when screened
- Primary neurological ICU admission diagnosis
- Patients discharged from the ICU following cardiac surgery
- Currently receiving or planned to receive end-of-life care
- Patient not expected by the clinical team to survive hospital discharge
- Patient with dialysis-dependent chronic renal failure prior to ICU admission

- Physical condition resulting in an inability to perform, a cardiopulmonary exercise test (CPET), for example, major limb trauma, amputation, or primary neurological injury (e.g. stroke, brain injury, Guillain-Barre syndrome).
- Any absolute or relative contraindication for CPET testing.
- Patient lacking mental capacity at the time of screening for eligibility
- Patients with previously adopted care escalation plan that excludes level 3 care
- Patients with a major physical disability that severely affects the activities of daily living before ICU admission

5.4 CO-ENROLMENT

Co-enrolment will occur with the ABC post-ICU trial. Other co-enrolment will be permitted only if it is in agreement with an ACCORD Co-enrolment Policy (POL008 Co-enrolment Policy).

6 PARTICIPANT SELECTION AND ENROLMENT

6.1 IDENTIFYING PARTICIPANTS

Patients discharged from the general ICU/HDU of the RIE and WGH will be screened for eligibility by doctors and nurses working in the Edinburgh Critical Care Research Group (ECCRG), who are part of the clinical critical care (direct care) team.

6.2 RECRUITMENT WINDOW

Eligible patients will be able to provide consent at any time following discharge from the ICU/HDU to hospital discharge.

6.3 CONSENTING PARTICIPANTS

In order to be involved in this study, participants must have the mental capacity to give consent and personally sign and date the latest approved version of the Informed Consent form before any study-specific procedures are performed.

Potentially eligible patients will be assessed for study suitability, including their capacity to make a decision. Capacity will be determined in consultation with the direct clinical team, who are caring for the patient. For those eligible for the cardiopulmonary exercise test, the ability to undertake it will be decided by the cardiopulmonary exercise testing team, who will conduct the cardiopulmonary test later within the study. Only after a favourable decision regarding the patient's suitability is received from both clinical and cardiopulmonary exercise testing teams, the first approach to the patient will be attempted. In the post-ICU/HDU wards, a member of the research team will conduct the initial patient approach at the earliest time when the patient regains the capacity to provide informed consent after ICU/HDU discharge.

Written versions of the Participant Information and Informed Consent form will be presented to the participants detailing the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects, and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The recruiting window for this study is anytime following ICU/HDU discharge. The participant will be given at least 24 hours to consider the information and the opportunity to question the investigator/research team and other persons to help decide whether they will participate in the

study. However, the final decision should be made within the recruitment window. Written informed consent will then be obtained. The person who obtained the consent will be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site, and a third record added to the patient record. The decision to participate will also be recorded in the patient's electronic medical record (TrakCare; Intersystems).

Two-three months after enrolment, participants will receive a letter describing the study and explaining their involvement, including any agreement to use their data for future research. They will be given the contact detail of the Edinburgh Critical Care research team and a reminder that they can opt out of this at any time.

Although absolute and relative contraindications for undertaking the cardiopulmonary exercise test were indicated in the study's exclusion criteria, to ensure the participant's safety and suitability for the cardiopulmonary exercise test, the participant will be approached and seen by a member of the cardiopulmonary exercise team who is employed by and work within the RIE cardiopulmonary exercise laboratory.

6.3.1 Withdrawal of Study Participants

During the study, a participant may choose to withdraw from the study at any time. Participants who no longer want to be involved in the study are under no obligation to provide a reason. Their medical care will not be compromised by the decision to withdraw from the study. The patient will be asked for permission to use his/her data that has been already collected and if the patient decides to restrict usage of the data further in the research, data will be deleted. In case when the participant loses capacity during the study, the already collected data will be preserved and used in the study, considering that the participant's legal representative is not against it.

7 STUDY ASSESSMENTS

7.1 STUDY ASSESSMENTS

After obtaining participant written consent, the baseline variables along with fatigue level and disabilities in daily living will be collected during inpatient care, whereas the accelerometery data will be recorded for some time after hospital discharge (for 2 months since enrollment). Participants will have the option of omitting the CPET test if they feel it is overly burdensome to them. In addition, hospital readmission rates during the first 3 months following hospital discharge will be extracted from the electronic medical records. Relevant study data will be obtained from the sources listed below:

- Patient medical records (baseline and follow up data).
- Raw data obtained from the wearable wrist accelerometer starting from the day of enrolment until the actigraphy device is removed and posted back. The acceleration data will be analysed using analytical software provided with the GENEActive wrist accelerometer.
- Cardiopulmonary exercise test variables. After assessing for the presents of potential contraindications within the period of 5 to 20 days after ICU discharge or before hospital discharge whichever occurs first, participants will try to undergo the CPET test in full compliance with the latest guidelines and recommendations by Levett and colleagues (2018) and will be reported in the standard CPET reporting form that is accepted by the RIE cardiopulmonary exercise laboratory (see: appendix). The pre-test assessment, testing, and supervision during the test will be conducted by the RIE cardiopulmonary exercise testing team.

- On the day of enrollment and then, only if more than 48 hours past since enrollment, on the day of the cardiopulmonary exercise test or close to the date of hospital discharge, participants will be asked to fill in questionnaires:
    1. Barthel Index form (appendix)
    2. VAS-F scale (appendix)

7.2 LONG TERM FOLLOW UP ASSESSMENTS

Participants will be followed until the wrist-worn accelerometer's battery needs a recharge which the manufacturer states to be 45 days if the recording frequency is set to low but the collaborator of our study Dr Athanasios Tsanas who has used this device in his research confirmed that the battery could hold a charge for up to 2 months. On this basis, we considered recording accelerometery data for as long as possible and have set the timing of the data recording for 2 months. The device will record the participant's activity, skin temperature, and ambient light intensity automatically during the whole study period. The recorded data extraction will be made once the device is returned. In addition, the research team will make attempts to reach the participants via telephone or mail to find out whether they have any issues related to the accelerometer device appliance and remind them about their involvement in the study.

7.3 STORAGE AND ANALYSIS OF SAMPLES

No biological samples will be collected.

8 DATA COLLECTION

8.1 At baseline

The following patient data will be collected by the investigator/research team from the NHS electronic patient record (TRAK)

- Demographics: gender, sex, age.
- Functional Comorbidity Index (FCI) which is calculated based on the presence or absence of the chronic diseases (18 diagnoses) before current ICU admission;
- Acute illness characteristics: ICU admission diagnosis; APACHE II score; duration of mechanical ventilation; duration of renal replacement therapy (if required); the worst SOFA score.
- Fatigue Severity Scale and Activity of Daily Living (at the time of enrolment).
- ICU related variables: neuromuscular blocker and corticosteroid drugs use.
- Laboratory findings: haemoglobin concentration.

8.2 During the study

Data will be collected from several sources. First, cardiopulmonary exercise capacity results will be taken from the CPET reporting form, which is used in the RIE cardiopulmonary exercise laboratory (see appendix). Second, questionnaire-based data regarding participants' fatigue severity and activities of daily living will be drawn from the inventory answered by participants. And third, accelerometery variables will be retrieved from the GENEActive device after receiving it from the participant.The timing and collected variables are summarised in Table 2 below.

Table 2. Timeline and variables collected during the study

Variables	Timing		
	At enrolment	5 to 20 days after ICU	60 days from enrolment

CPET		+	
Anaerobic threshold (AT) (ml min $^{-1}$ and ml kg^{-1} min^{-1})		+	
Peak O_2 uptake (VO_2peak) (ml min^{-1} and ml kg^{-1} min^{-1})		+	
Peak work rate (WRpeak) (W)		+	
VE - VCO_2 slope ($\Delta VE/\Delta VCO_2$)		+	
Questionnaires	+	+	
VAS-Fatigue	+	+	
Barthel Index	+	+	
Actigraphy (accelerometer)	+	+	+
Sleep duration (minutes\night)	+	+	+
Night-time movement/non-movement	+	+	+
Waking episodes	+	+	+
Free-living physical activity (minutes/day)	+	+	+
Light physical activity (min)	+	+	+
Moderate physical activity (min)	+	+	+
Vigorous physical activity (min)	+	+	+
Sedentary behaviour time (min)	+	+	+

8.3 Following the study

The data regarding hospital readmission within 3 months since hospital discharge will be extracted from the routinely available electronic medical records system (TRAK).

- Hospital admissions rate following current discharge

8.4 Source Data Documentation

- Electronic medical records
- CPET report
- Questionnaires
  - Barthel Index form
  - Visual Analogue Scale – Fatigue
- Accelerometer device

8.5 Case Report Forms

All participants' data will be entered into the excel database.

9 DATA MANAGEMENT

9.1 Personal Data

The following personal data will be collected as part of the research:

Demographic data:

- Age
- Gender

Anthropometric data:

- Height
- Weight
- BMI

Laboratory findings:

- Haemoglobin concentration

Community Health Index (to contact participant's GP)

Contact details:

- Name/surname, home address, telephone number

The contact details will be used solely to organize the collection of the wrist-worn accelerometer towards the end of the second month after hospital discharge.

The personal data (UHPI) will be stored by the research team on a dedicated, encrypted excel spreadsheet or specially created access database and stored on NHS Lothian managed computers. In addition, the electronic data file will be password-locked. The paper-based participants' information (consent form, answered questionnaires, CPET report) will be stored in the locked cupboard within the personnel-only, lockable room at the Royal Infirmary Edinburgh (NHS Lothian site). Sensitive participants' data will not leave this location and will be destroyed 12 months after the completion of the data collection. Only anonymised data will be subjected to long-time storage (10 years) and analysis that will take place within the University of Edinburgh managed computers/network.

9.2 Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

9.3 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers.

9.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

The study is an exploratory study associated with the ABC post-ICU trial. The estimated recruitment to the ABC post-ICU trial at the Edinburgh Royal Infirmary is 2 patients per month. The trial aims to recruit for at least 18 months but is likely to be prolonged by the impact of the COVID pandemic. Total recruitment is likely to be 35-40 patients within groups 2 and 3 of this study. Assuming around 50% of patients agree to participate in this additional study, a feasible recruitment target is 20 patients (10 from each randomisation group). We will aim to recruit up to 20 patients in the other two groups over the same period. The total target sample size will be 40 patients.

10.2 PROPOSED ANALYSES

A study analysis plan will be written before any analyses are undertaken.

A description of the entire cohort, length of stay, the progression of fatigue, activities of daily living over the follow-up period along with obtained objective measures of cardiopulmonary fitness, sleep pattern, daytime activity, circadian rhythms regularity and subgroups of interest (e.g ICU-AW vs No ICU-AW, had RBC transfusion vs had not) will be reported with appropriate summary measures (mean (SD), median (IQR), or n (%)).

Comparative analysis between observed groups depending on sample distribution pattern will be analysed by One-way ANOVA/Kruskal-Wallis test or unpaired T-test/Mann-Whitney test. Associations between the feeling of fatigue, daily activity, sleep pattern and functional status will be explored using correlation and regression analyses. Also, a correlation between ICU related variables, hospital readmission rate and study primary outcomes if present will be reported. These analyses will take into account the exploratory nature of the study.

11 ADVERSE EVENTS

Generally, a cardiopulmonary exercise test is a safe procedure even among the high-risk population with contraindications for this procedure. The adverse events rate reported by some authors is 0.04%- 0.16% with no fatal cases (Skalski, Allison, & Miller, 2012), (Gibbons et al., 2002) and varies with the patients population. Nonetheless, any adverse events during the study will be reported according to ACCORD recommendations. The adverse events during the CPET might be classified as minor and major. Major adverse events include death within 48 hours of the stress test, external defibrillation or implantable cardioverter-defibrillator discharge, sustained VT (wide complex tachycardia lasting longer than 30 seconds), myocardial infarction, syncope, administration of advanced cardiac life support medications, referral for direct hospital admission, or referral to an emergency department, orthopaedic injury. All other adverse events that do not require hospital admission or prolong current hospital stay are considered minor and usually resolves with rest and without additional treatment.

Every cardiopulmonary exercise test will take place in the cardiopulmonary exercise test laboratory designed according to accepted standards of care, equipped with all necessary emergency equipment, and will be supervised by two clinicians experienced in conducting the CPET who are qualified in the basic and advanced life support along with the expertise in early identification of the signs of potential adverse events during the test. On the day of the testing, participants will be asked to wear comfortable clothes, refrain from eating solid foods for 2 hours, caffeine and smoking at least for 8 hours before the test. Immediately before the test, the participant and his/her medical records will be re-assessed for potential contraindications for the test. During the test participant will be subjected to close haemodynamic monitoring which includes continuous 12 leads ECG, arterial blood pressure every 2-3 minutes, expiratory gas content, and minute ventilation on a breath by breath basis. The test will be immediately stopped in case of any signs of a possible adverse event and the participant will be treated accordingly. Every adverse event will be reported according to ACCORD's recommendation.

It is known that some questionnaires or interviews conjuring grim memories or experiences might provoke emotional distress among research participants. Although questionnaires that are intended to be used in this study neither harbour distressing potential nor have been mentioned in the literature to be related to participants upset, the research team will remain vigilant in regards to participants' emotional status during the study and provide psychological support, seeking further advice from the emotional and psychologic support within the NHS if needed.

12 OVERSIGHT ARRANGEMENTS

12.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s) as required. In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if an audit by the ACCORD QA group is required. Should an audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).
Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

13.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of the study site staff.

13.2.1 Informed Consent

The Investigator will be responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research will be voluntary and based on a clear understanding of what is involved.

Participants will receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person (the member of the research team) and will cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time (minimum of 24 hours) to consider the information provided. It will be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. Assuming the duration of the study (2 months) and the consent given following a critical illness episode, a reminder letter will be sent to the participants during the second

month of the study describing the study, their role in it, and the data which are collected, stressing the possibility to withdraw from the study anytime.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the research team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

13.2.2 Study Site Staff

The Investigator will be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

13.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

13.2.5 GCP Training

All researchers will undertake GCP training in order to understand the principles of GCP. GCP training status for all investigators will be indicated in their respective CVs.

13.2.6 Confidentiality

All evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

13.2.7 Data Protection

Personal data (UHPI) will be stored by the research team on a dedicated MS Excel spreadsheet/MS access database and stored on a secure NHS Lothian servers/computers. This spreadsheet will be the only link between the patient record and the research database and will not leave the NHS server. Data stored in the research database will be anonymized prior to transferring and storage on the University of Edinburgh computer/servers. In order to enhance data security, all data will be subjected to encryption and a strong password will be set. Password strength: AT LEAST 9 CHARACTERS IN LENGTH and must consist of AT LEAST one lower-case letter, one upper-case letter, and one number. Besides, it will be known only to the chief investigator.

STUDY CONDUCT RESPONSIBILITIES

13.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

13.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

13.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

13.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.7 END OF STUDY

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

This is not applicable to this study.

13.9 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. All publications and academic outputs will recognize the contributions made by the researchers involved in the project.

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16 APPENDIXES

16.1 The Barthel Index

Barthel Index of Activities of Daily Living

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

Bowels 0 = incontinent (or needs to be given enemata) 1 = occasional accident (once/week) 2 = continent Patient's Score: _____	**Transfer** 0 unable – no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent Patient's Score: _____
Bladder 0 = incontinent, or catheterized and unable to manage 1 = occasional accident (max. once per 24 hours) 2 = continent (for over 7 days) Patient's Score: _____	**Mobility** 0 = immobile 1 = wheelchair independent, including corners, etc. 2 = walks with help of one person (verbal or physical) 3 = independent (but may use any aid, e.g., stick) Patient's Score: _____
Grooming 0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided) Patient's Score: _____	**Dressing** 0 = dependent 1 = needs help, but can do about half unaided 2 = independent (including buttons, zips, laces, etc.) Patient's Score: _____
Toilet Use 0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping) Patient's Score: _____	**Stairs** 0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent up and down Patient's Score: _____
Feeding 0 = unable 1 = needs help cutting, spreading butter, etc. 2 = independent (food provided within reach) Patient's Score: _____	**Bathing** 0 = dependent 1 = independent (or in shower) Patient's Score: _____

Total score _____

Scoring: Sum the patient's scores for each item. Total possible scores range from 0 – 20, with lower scores indicating increased disability. If used to measure improvement after rehabilitation, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable.

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(Collin et al., 1988)

Guidelines for the Barthel Index of Activity of Daily Living General

- The Index should be used as a record of what a patient **does**, NOT as a record of what a patient **could do**.

- The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
- The need for supervision renders the patient not independent.
- A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives, and nurses will be the usual source, but direct observation and common sense are also important. However, direct testing is not needed.
- Usually the performance over the preceding 24 – 48 hours is important, but occasionally longer periods will be relevant.
- Unconscious patients should score '0' throughout, even if not yet incontinent.
- Middle categories imply that the patient supplies over 50% of the effort.
- Use of aids to be independent is allowed.

Bowels (preceding week)
- If needs enema from nurse, then 'incontinent.'
- 'Occasional' = once a week.

Bladder (preceding week)
- 'Occasional' = less than once a day.
- A catheterised patient who can completely manage the catheter alone is registered as 'continent.'

Grooming (preceding 24 – 48 hours)
- Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements can be provided by helper.

Toilet use
- Should be able to reach toilet/commode, undress sufficiently, clean self, dress, and leave.
- 'With help' = can wipe self and do some other of above.

Feeding
- Able to eat any normal food (not only soft food). Food cooked and served by others, but not cut up.
- 'Help' = food cut up, patient feeds self.

Transfer
- From bed to chair and back.
- 'Dependent' = NO sitting balance (unable to sit); two people to lift.
- 'Major help' = one strong/skilled, or two normal people. Can sit up.
- 'Minor help' = one person easily, OR needs any supervision for safety.

Mobility
- Refers to mobility about house or ward, indoors. May use aid. If in wheelchair, must negotiate corners/doors unaided.
- 'Help' = by one untrained person, including supervision/moral support.

Dressing
- Should be able to select and put on all clothes, which may be adapted.
- 'Half' = help with buttons, zips, etc. (check!), but can put on some garments alone.

Stairs
- Must carry any walking aid used to be independent.

Bathing
- Usually the most difficult activity.
- Must get in and out unsupervised, and wash self.
- Independent in shower = 'independent' if unsupervised/unaided.

(Collin et al., 1988)

16.2 VAS-F

Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F)

ID# _____ Date _____ Time _____ a.m. _____ p.m.

We are trying to find out about your level of energy before and after your night of sleep. There are 18 items we would like you to respond to. This should take less than 1 minute of your time. Thank you.

DIRECTIONS: You are asked to circle a number on each of the following lines to indicate how you are feeling RIGHT NOW.

For example, suppose you have not eaten since yesterday.

What number you would circle below?

not at all **hungry**	0 1 2 3 4 5 6 7 8 9 10	extremely **hungry**

You would probably circle a number closer to the "extremely hungry" end of the line.

This is where I put it:

not at all **hungry**	0 1 2 3 4 5 6 7 **(8)** 9 10	extremely **hungry**

NOW PLEASE COMPLETE FOLLOWING ITEMS:

1.	not at all **tired**	0 1 2 3 4 5 6 7 8 9 10	extremely **tired**
2.	not at all **sleepy**	0 1 2 3 4 5 6 7 8 9 10	extremely **sleepy**
3.	not at all **drowsy**	0 1 2 3 4 5 6 7 8 9 10	extremely **drowsy**
4.	not at all **fatigued**	0 1 2 3 4 5 6 7 8 9 10	extremely **fatigued**
5.	not at all **worn out**	0 1 2 3 4 5 6 7 8 9 10	extremely **worn out**
6.	not at all **energetic**	0 1 2 3 4 5 6 7 8 9 10	extremely **energetic**
7.	not at all **active**	0 1 2 3 4 5 6 7 8 9 10	extremely **active**
8.	not at all **vigorous**	0 1 2 3 4 5 6 7 8 9 10	extremely **vigorous**
9.	not at all **efficient**	0 1 2 3 4 5 6 7 8 9 10	extremely **efficient**
10.	not at all **lively**	0 1 2 3 4 5 6 7 8 9 10	extremely **lively**
11.	not at all **bushed**	0 1 2 3 4 5 6 7 8 9 10	extremely **bushed**
12.	not at all **exhausted**	0 1 2 3 4 5 6 7 8 9 10	extremely **exhausted**
13.	**keeping my eyes open** is no effort at all	0 1 2 3 4 5 6 7 8 9 10	**keeping my eyes open** is a tremendous chore

14. **moving my body** is no effort at all	0	1	2	3	4	5	6	7	8	9	10	**moving my body** is a tremendous chore
15. **concentrating** is no effort at all	0	1	2	3	4	5	6	7	8	9	10	**concentrating** is a tremendous chore
16. **carrying on a conversation** is no effort at all	0	1	2	3	4	5	6	7	8	9	10	**carrying on a conversation** is a tremendous chore
17. I have absolutely **no desire to close my eyes**	0	1	2	3	4	5	6	7	8	9	10	I have a tremendous **desire to close my eyes**
18. I have absolutely **no desire to lie down**	0	1	2	3	4	5	6	7	8	9	10	I have a tremendous **desire to lie down**

References

1. *Lee, K.A., Hicks, G. & Nino-Murcia, G., 1991. Validity and reliability of a scale to assess fatigue. Psychiatry Research, 36(3), pp.291–298.*
2. *Lachapelle, D.L. & Finlayson, M.A.J., 1998. An evaluation of subjective and objective measures of fatigue in patients with brain injury and healthy controls. Brain Injury, 12(8), pp.649–659.*

16.3 Cardiopulmonary exercise test

Cardiopulmonary exercise testing (CPET) provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function (American Thoracic and American College of Chest, 2003). At the core of this method lies the difference in inhaled and exhaled gas content with respect to oxygen and carbon dioxide measured on breath by breath basis under gradually increasing strenuous activity (Levett et al., 2018) The CPET is used to give an objective assessment of individual exercise capacity and reveal the possible source of exercise limitation which might be used both as a diagnostic and prognostic tool. It should be noted that an indication and utilization of this procedure are constantly expanding.

Indications:

Grade B

1. To predict the post-operative morbidity and mortality.
2. To guide clinical decisions about the most appropriate level of perioperative care.
3. To identify previously unsuspected pathology
4. To evaluate the effects of neoadjuvant cancer therapies including chemotherapy and radiotherapy
5. To guide prehabilitation and rehabilitation training programmes.

Grade C

1. To inform the processes of multidisciplinary shared decision-making and consent
2. To direct pre-operative referrals/interventions to optimize comorbidities

Grade D

1. To guide intraoperative anaesthetic practice

Contraindications:

Absolute and relative contraindications for CPET (adapted from American Thoracic Society (American Thoracic and American College of Chest, 2003)). Patients with relative contraindications should be discussed with an appropriate clinician and the risks and benefits of testing evaluated. Patients with relative contraindications should be directly supervised by a physician

Absolute contraindications	Relative contraindications

Acute myocardial infarction (3-5 days) Unstable angina Uncontrolled arrhythmia causing symptoms or haemodynamic compromise Syncope Active endocarditis Acute myocarditis or pericarditis Symptomatic severe aortic stenosis Uncontrolled heart failure Suspected dissecting or leaking aortic aneurysm Uncontrolled asthma Arterial desaturation at rest on room air <85%	Untreated left main stem coronary stenosis Asymptomatic severe aortic stenosis Severe untreated arterial hypertension at rest (>200 mm Hg systolic, >120 mm Hg diastolic) Tachyarrhythmias or bradyarrhythmias Hypertrophic cardiomyopathy Significant pulmonary hypertension Thrombosis of the lower extremity until treated for a minimum of 2 weeks Within 2 weeks of acute symptomatic pulmonary embolus Abdominal aortic aneurysm >8.0 cm Electrolyte abnormalities Advanced or complicated pregnancy

Service structure and supervision

A CPET should be carried out by at least two practitioners, one of those must be an expert in CPET who has a complete understanding of equipment operation, test protocols, physiology, and pathophysiology of exercise. In addition, they must be able to identify and immediately manage any complications and adverse event which might occur during the exercise test as well as all indications for premature test termination. One of the test practitioners should have current intermediate life support skills and the other a minimum of current basic life support with automated external defibrillator competence and advanced life support resuscitation team should be immediately available. In the case of either high-risk CPET tests or test-taker who have any relative contraindication listed above have to be directly supervised by a physician. In terms of CPET expertise development, it is recommended to get Perioperative Exercise Testing & Training Society (POETTS) accreditation as well as perform and interpret at least 25 tests per year to maintain CPET expertise.

Preparation for the exercise test

Individuals intended to undertake this procedure should be given all possible information on the CPET process, risks, and benefits. This process may involve formal written consent. Test-takers should not withhold their regular medication but avoid caffeine, alcohol, cigarettes, and strenuous exercise on the day of testing as well as should not eat for 2 hours prior to the test whereas to drink water is allowed.

Risk of adverse events

CPET is a relatively safe investigation, especially in individuals with no comorbidity. Although high-risk individuals with underlying cardiac comorbidities have greater risk of adverse events, it is still very low with major adverse events rate less than 1 per 1000 tests and the majority of it resolves by itself (Dhoble et al., 2012; Keteyian et al., 2009; Kim et al., 2019). To date, no deaths have been reported during perioperative CPET in the UK.

CPET equipment

The CPET laboratory should be equipped with:

- Mechanically or electronically braked cycle ergometer (the latter is preferable for precise work-rate estimation)
- Airflow or Volume-transducing device
- Pneumotachograph

- Gas analysers capable of detecting the ventilatory gases (O2, CO2) concentration at breath by breath basis with a response time less than 90 ms
- Monitor capable of continuous monitoring of pulse oximetry, non-invasive blood pressure, and 12 lead electrocardiography
- Oxygen supply
- First aid kit
- Automated electronic defibrillator
- Primary resuscitation equipment
- Baseline data collection
- Baseline data with respect to age, gender, body weight and height should be routinely collected. Detailed patient's medical history should be examined focusing on potential contraindications, cardiovascular disease, drug history and laboratory findings.

Exercise protocol

There are several CPET protocols. The main difference between them resides in how the workload is applied.

- a progressive incremental exercise or continuous ramp protocol where the load is increased every minute till the limits of tolerance (frequently used);
- a multistage exercise protocol;
- a constant work rate;
- a discontinuous protocol (rarely used in clinical settings);

The progressive incremental exercise test consists of a 4 consequent phases;

1. Rest phase (3-5 minutes) when resting data are recorded;
2. Unloaded pedalling (3-5 minutes) during which participant adapts to maintain pedal cadence within the range of 55-75rpm (usually 60rpm);
3. Incremental/Ramp phase (8-12 minutes) when the pedal resistance gradually intensifies at the rate of 5 to 25 W/minute;
4. Recovery phase (5-10 minutes) while the pedal load is removed, and the participant continues to pedal to prevent venous pooling in the lower extremities. Cardio monitoring is prolonged until the heart rate reaches the baseline level.

The main variables obtained from the CPET are summaries in the table below

Key response variables reported for cardiopulmonary exercise testing adapted from Levett et al (Levett et al., 2018)**.**

Exercise capacity variables

- Anaerobic threshold (AT) (ml min $^{-1}$ and ml kg^{-1} min^{-1})
- Peak O2 uptake (VO2peak) (ml min^{-1} and ml kg^{-1} min^{-1})
- Peak work rate (WRpeak) (W)

Cardiorespiratory variables

- VO2-work rate slope (ΔDVO2/ΔDWR) (ml min $^{-1}$ W^{-1})
- Heart rate (HR) (beats min^{-1}) - resting and peak exercise
- Heart rate reserve (HR) (beats min^{1}) - peak exercise = maximum predicted heart rate - measured maximum heart rate
- Oxygen pulse (ml beat $^{-1}$) - resting and peak exercise
- Arterial blood pressure (BP; mm Hg) - resting and peak exercise
- Arterial O_2 saturation (SpO2;%) - resting and peak exercise
- Tidal volume (V_T) (l or ml) - resting and peak exercise
- Respiratory rate (RR) (bpm) - resting and peak exercise
- Ventilation (VE) (litres min^{-1}) - resting and peak exercise
- Breathing reserve (BR) (litres min^{-1} and % of VE at peak exercise) (BR = MVV-VEpeak)
- Ventilatory equivalent for O_2 (VE/VO2) at AT or minimum value
- Ventilatory equivalent for CO2 (VE/VCO2) - at AT or minimum value
- VE - VCO2 slope (ΔVE/ΔVCO$_2$) (particularly if no definite AT identified)
- End-tidal partial pressure of O_2 (P_{ETO_2} mm Hg) - resting and peak exercise
- End-tidal partial pressure of CO_2 (P_{ETCO_2} mm Hg) - resting and peak exercise

Spirometry variables (resting)

- Forced expiratory volume in 1 s (FEV_1) (l)
- Forced vital capacity (FVC) (l)
- Maximum voluntary ventilation (MVV) d directly measured or estimated as FEV1x35-40 (litres min^{-1})
- Inspiratory capacity (IC) (l)

Indications for stopping the test

Although the participant is encouraged to exercise up to the limits of their endurance, the exercise test might be terminated at any phase due to either symptom limitation or clinically inappropriate symptoms onset.

Indications for CPET termination are listed in the table below

Indications for the premature termination of an exercise test (adapted from American Thoracic Society(American Thoracic and American College of Chest, 2003)

Angina

- >2 mm ST depression if symptomatic or 4 mm if asymptomatic or >1 mm ST elevation
- Significant arrhythmias causing symptoms or haemodynamic compromise
- Fall in systolic blood pressure >20 mm Hg from the highest value during the test
- Hypertension >250 mm Hg systolic; >120 mm Hg diastolic
- Severe desaturation: SpO_2 <80% (lower may be accepted in patients with known underlying lung disease)
- Loss of coordination
- Mental confusion
- Dizziness or faintness

The sample CPET reporting form that will be used in this study is presented on the next page.

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Cardiopulmonary Exercise Testing Report

Patient Details: Name: DoB: Consultants:
CHI: UHPI:

Indication: Date of Test:

Demographics: Age: Sex: Male
Weight: kg Height: m BMI:

Protocol: Ergometer: RER:
Ramp: Data Quality

Centile*

Exercise: Anaerobic Threshold: ml/min/kg
VO2 peak: ml/min/kg % Predicted
Peak work-load: Watts METS
O2/work load: ml/min/Watt
Exercise duration: min:sec Senior Physiologist:
Exercise limitation: Leg discomfort

Cardiovascular: Resting ECG: Sinus rhythm
Heart Rate: (rest) (peak) % Predicted (Peak)
Oxygen Pulse: ml
Exercise induced ischaemia/arythmia:

Ventilatory: Resting SpO2: % Desaturation on exercise:
Breathing Reserve %
VE/VCO2:

Summary:

Reported by:

* Centile: Values quoted relative to patient assessment cohort

Report Printed:

16.4 Accelerometery device

"GENEActiv" is a wrist-worn accelerometer device that designed to objectively measure an individual's lifestyle behaviour by recording the speed and amplitude of a limb movement on three axes. The data obtained could be used to improve healthcare strategies and for research purposes. In addition, all collected data are only about movement, skin temperature, and ambient light intensity without any personal information and location. It is worth mentioning that this device has been used in an array of scientific healthcare researches and has been validated in different population groups (Alharbi et al., 2016; Baldwin et al., 2019; Duncan et al., 2016; Schwab et al., 2019). More information are available at (https://www.activinsights.com/technology/geneactiv/).

The detailed description of the "GENEActive" wrist-worn accelerometer is summarised below

100% water-resistant body frame made of medical grade plastic that weighs 16g and PU resin strap. This device complies with part 15 of the FCC Rules and with the Directive 2004/108/EC; tested to BS EN 61000-6-1:2007 and BS EN 61000-6-3:2007.

Equipped with:

- ambient light sensor to map the environment (indoor or outdoor)
- body temperature sensor to determine whether the device is being worn (confirm wear time)
- three-axle accelerometer sensor with Logging Frequencies from 10 to 100 Hz
- quartz internal real-time clock
- 0.5G of data storage
- rechargeable battery lasting up to 45 days (depending on recording frequency)
- USB port for data extraction
- Open source analytics software with open software development kit which allows creating your own data analysis algorithms