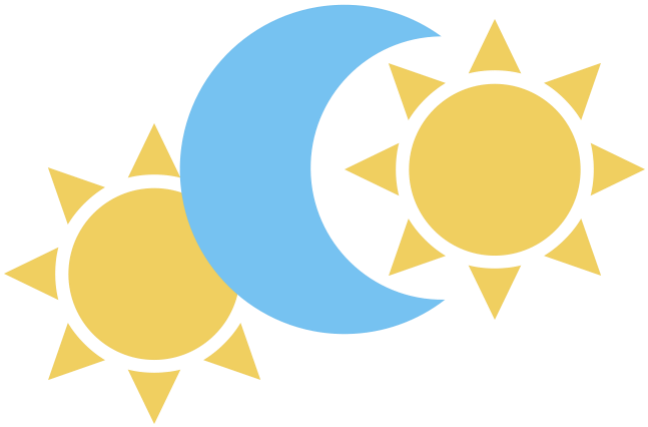
A feasibility randomised controlled trial of administering daytime only enteral feeding compared to standard continuous enteral feeding, to reduce delirium in mechanically ventilated, critically ill adults, with qualitative and circadian mechanistic sub-studies.

DAYDREAM



Short trial title/Acronym:

DAytime onl**Y** fee**D**ing c**R**itical illn**E**ss **A**nd deliriu**M** trial

(**DAYDREAM** trial)

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ISRCTN	
FUNDER'S Reference	**NIHR207910**
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This protocol has regard for the HRA guidance and order of content

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018, the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
APACHE II	Acute Physiology and Chronic Health Evaluation II
AR	Adverse Reaction
CAM-ICU	Confusion Method for ICU
CI	Chief Investigator
CEF	Continuous Enteral Feeding
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DoF	Daytime Only Feeding
eCRF	Electronic Case Report Form
EQ5-5D-5L	The 5-level EQ-5D version (the EuroQol Group, 2009)
ESPEN	European Society for Clinical Nutrition and Metabolism
GRV	Gastric Residual Volume
GCP	Good Clinical Practice
HRA	Health Research Authority
ICNARC	Intensive care national audit and research centre
ICU	Intensive Care Unit
IPAT	Intensive Care Psychological Assessment Tool
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
NHS	National Health Service
PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PTSD	Post Traumatic Stress Disorder

PTSS-14	Post Traumatic Stress Syndrome 14 Questions Inventory
QA	Quality Assurance
R&D	Research & Development
RASS	Richmond Agitation Scale
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RWPC	Research Without Prior Consent
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUH	Southampton University Hospitals
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
UHP	University Hospital Plymouth NHS Trust
VAP	Ventilator Associated Pneumonia

Trial Summary

Trial Title	A feasibility randomised controlled trial of administering daytime only enteral feeding compared to standard continuous enteral feeding, to reduce delirium in mechanically ventilated, critically ill adults, with qualitative and circadian mechanistic sub-studies
Internal ref. no. (or short title)	**DA**ytime only fee**D**ing c**R**itical illn**E**ss **A**nd deliriu**M trial** **DAYDREAM trial**
Trial Design	Multi-centre, feasibility randomised controlled trial
Participants	
Trial Participants	Critically ill adults admitted to an intensive care unit requiring enteral feeding
Eligibility Criteria	**Inclusion criteria** • Adults (aged 18 years and above) • Unplanned admission to ICU within 48 hours of admission • Mechanically ventilated, with clinical view it will be for > 24 hours

	• Plan to start enteral feeding or enteral feeding has commenced during the daytime only so far • Likely to require enteral feeding for > 48 hours **Exclusion criteria** • Planned admissions unless unexpectedly ventilated during first 24 hours of admission. • Continuous enteral feeding already commenced overnight (22:00-08:00) • Known intolerance to enteral feeding or currently unable to tolerate enteral feed • Post-emergency bowel surgery • Type 1 diabetes or pre-existing insulin therapy (with risk of significant dysglycaemia on fasting for 10 hours) • Hyponatraemia; serum Na < 115 mmol/L • Nil-by-mouth • Clinician considers daytime only feeding unsuitable for the patient • Pregnancy and breast feeding • Post-pyloric feeding via jejunostomy tube • Receiving parenteral nutrition • Dementia, psychosis, bipolar disorder and pre-existing use of antipsychotic drugs (haloperidol, olanzapine, quetiapine) or alcohol use, daily and to excess. • Prone position ventilation
Planned Sample Size	40 in total across both (University Hospital Plymouth NHS Trust ICU and Southampton University Hospitals Trust ICU) sites
Study Treatment	
Study Intervention arm	Enteral feeding given in the daytime only over 14 hours, between 08:00 and 22:00 Type of feed and its volume individualised to each patient as per standard feeding practice.
Study Control arm	Enteral nutrition provided over 24 hours as per usual practice. Type of feed and its volume individualised to the patient as is usual care.
Treatment duration	Maximum 30 days
Follow up duration	90 days post recruitment into DAYDREAM
Planned Trial Period	Set up 6 months, recruitment 12 months, follow up 3 months, data analysis and reporting 3 months. Total 24 months
Objectives	

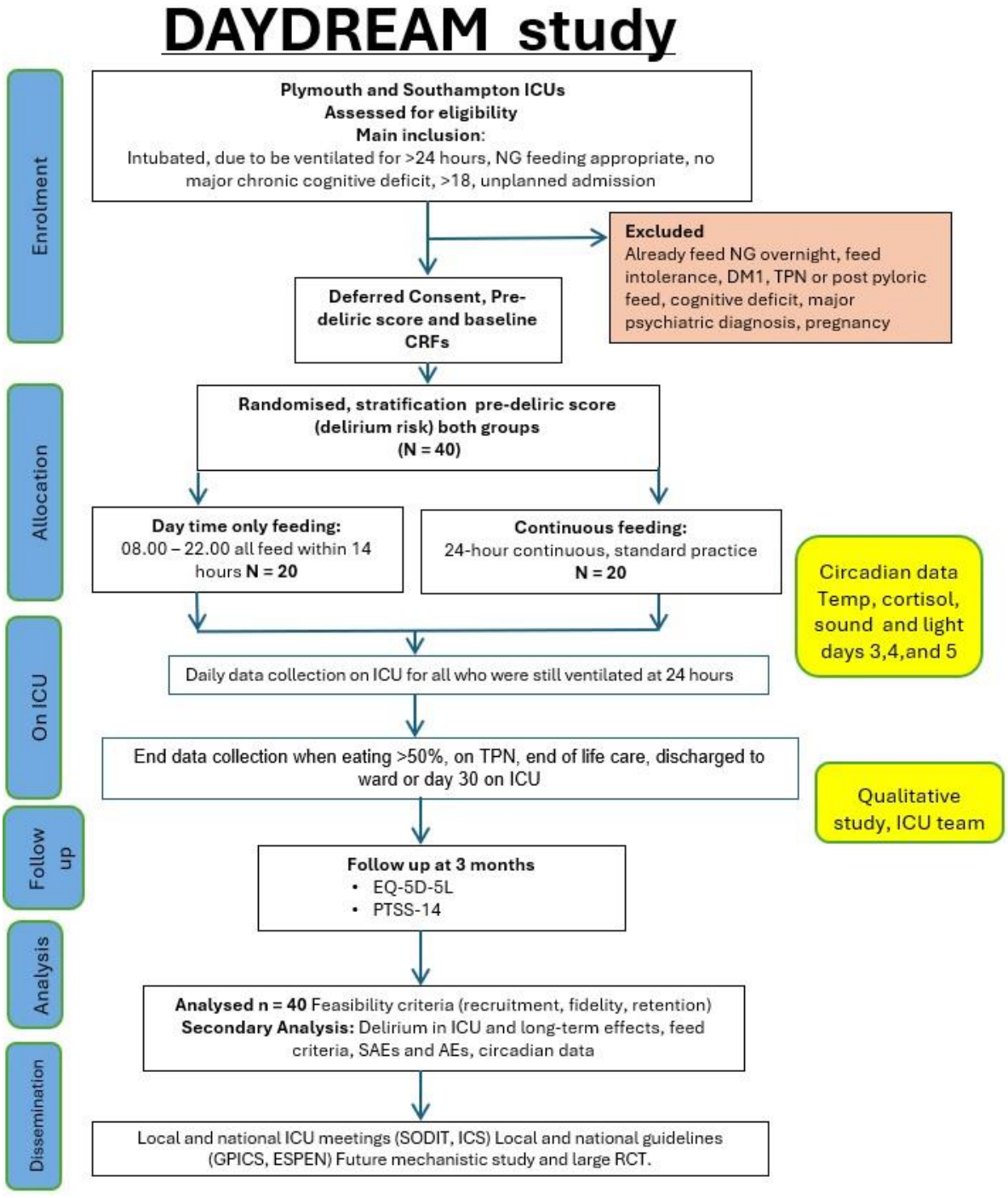
Primary objective	To conduct a randomised feasibility study of DoF compared to continuous feeding in critically ill patients who have been admitted to ICU for up to 30 days post-randomisation (during ICU stay only).
Feasibility objectives	1. Estimate rates of screening, recruitment and randomisation rates. 2. To ascertain retention and dropout rate (due to treatment and or trial demands). 3. To determine the fidelity of delivering DoF in adult critically ill patients. 4. Ascertain completeness of data collection throughout the trial including 90 days follow-up. 5. Acceptability of outcome measures 6. Identify intervention and trial barriers and develop methods to overcome these through a qualitative sub-study. See sub-study 1.
Secondary objectives	1. Collection of high-quality data to inform a future efficacy / effectiveness randomised controlled trial, including appropriate outcome measures 2. To monitor whether there are any additional safety issues when using daytime only feeding compared to 24-hour feeding. 3. To collect data on the long term psychological and functional impact of daytime feeding using the EQ5 DL and the PTSS-14.
Sub-study 1 Qualitative Evaluation	1. To identify potential barriers to successful delivery of daytime feeding 2. to evaluate and modify the educational package used in the future definitive daytime only feeding trial. 3. To evaluate the acceptability of the outcome measures
Sub-study 2 Mechanistic evaluation	To obtain data on circadian rhythms collecting a range of markers. • Serum cortisol • Serum mRNA • Body temperature • Light and sound exposure

Funding and Support in Kind

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
National Institute for Health and Care Research, Research for Patient Benefit Ref: NIHR207910	**£301,140**
Peninsula Medical Foundation, to fund an mRNA mechanistic bolt-on study of mRNA	**£10,000**

expression with mathematical analysis (ClinCirc)	

Fig 1. Study flowchart



1. BACKGROUND

The intervention: daytime only feeding (DoF)

Optimal nutrition is essential to critically ill patients. The standard method of providing enteral nutrition on intensive care units (ICUs) is continuously (24 hours per day) infusing liquid feed by a pump via a nasogastric tube. Whilst convenient, this contrasts with usual human physiology and may be detrimental to health. Continuous feeding prevents the potential benefits of a normal night-time fast,[1] and is disruptive to circadian function.[2] This may lead to a disrupted sleep-wake cycle, which is known to cause delirium.[3] Many factors contribute to the development of delirium in ICUs, and disturbance of normal circadian rhythm is one of them[4]. Several factors help to maintain circadian health, including light, feeding and exercise. Circadian rhythms can be entrained by feeding times[5–8].

We hypothesise that DoF in critically ill patients will improve circadian rhythms and so reduce the incidence of delirium.

In the UK, there are approximately 200,000 critically ill patients admitted to general adult ICUs each year. They have a wide range of diagnoses and pathologies, but all are at risk of multi-organ failure.[9] They also have a high risk of developing delirium, which occurs in >80% of those receiving mechanical ventilation[10] (a common intervention required by the critically ill).

Circadian rhythm and health

In health, biological functions exhibit predictable fluctuations over a 24-hour period, referred to as 'circadian rhythms'. This is the anticipatory oscillation in cellular and bodily function which optimises our ability to exercise or sleep at different times of the day. It is coordinated centrally in the brain and results in time-related secretion of melatonin, which enables coordinated cellular function.[11] Circadian rhythm is influenced by exposure to light, exercise, touch, social contact and feeding.

Circadian rhythm is influenced by time of feeding

In animal models, time of feeding has been shown to affect circadian patterns independently to light.[6, 12,13,] It is not known if the time of feeding in ICU patients will affect or re-synchronise circadian rhythms. This uncertainty is central to the study.

Disrupted circadian rhythm is associated with delirium

In critically ill patients, there is disruption in the normal 24-hour patterns of melatonin and cortisol secretion with less circadian fluctuation in vital signs and abnormal sleep-wake patterns[14]. In ICU patients, loss of the circadian fluctuation of melatonin and cortisol is associated with more delirium than when it is preserved.[4] We hypothesise that a contributor to delirium in the critically ill is the common practice of providing enteral feed continuously, day and night, so disrupting normal circadian health and hence contributing to delirium.

Daytime only feeding (DoF) in critically ill patients – evidence and outcomes

We have conducted a scoping review (in accordance with the Johanna Briggs Institute methodology[15]) of daytime only or time-restricted feeding in critically ill patients[16]. Patterns of the provision of feeding included continuous, cyclical and bolus feeding, all with a nighttime pause of at least 6 hours. We searched 6 databases, to produce 918 records that were screened by two independent reviewers. 15 studies met the inclusion criteria, including a total of 958 patients, with night-fasting time periods of 6 to 12-hours.

DoF in ICU, summary of the findings of the 14 studies in which DoF in the critically ill was delivered:

- Gastric or feeding intolerance is defined by European Society for Clinical Nutrition and Metabolism (ESPEN) international guidance as worsening gastrointestinal function with raised gastric residual volumes, or a failure to reach nutritional targets and gastrointestinal symptoms in response to feeding attempts[17]. Feeding intolerance, with varying definitions, was assessed in six studies [18–23]. DoF led to less constipation and no other differences.
- Nutritional goals were measured in four studies[19,20,23,24]. The volume of feed delivered was less with DoF[23,24] although patients received over 80% of their target volume.
- Bacterial colonisation and the incidence of ventilator associated pneumonia (VAP), was assessed in two studies [25,26], with no differences seen between groups.
- In terms of metabolic biomarkers: no difference in glucose levels[27] and respiratory quotient (RQ)[28] with DoF. DoF was associated with an increase in ketosis[24,28] bilirubin and insulin-like growth factor-1[27] levels (markers of fasting).
- Two studies measured temperature[29] and cortisol[30] at different time points over 24 hours in patients fed either only in the day or only at night. The time of feeding was associated with the peaks in temperature and cortisol, however, both studies had very small cohorts.

One study was in critically ill children who had an 8-to-12-hour nighttime fast, with a primary outcome of ketosis and detailed secondary outcomes relating to nutritional delivery[23]. The fasted group received less feed, but within the 80% nutritional target, which was limited by the prescribed feed. This informed our study in that we plan to use catch-up feeding to optimise nutritional delivery in both groups. A 12 hour fast was safe in critically ill children; we plan to use a 10 hour fast in adults.

Known benefits of a night-time fasting period

In health, a fasting period induces muscle synthesis, ketogenesis, and activation of autophagy.[31–34] These would all be beneficial to critically ill patients.

2. RATIONALE

In a future definitive trial, the primary research question will be: In mechanically ventilated and enterally fed critically ill adults, will DoF reduce the incidence of delirium during critical illness in the ICU compared to continuous feeding?

While there is evidence to support a proof of concept for DoF in the critically ill being a safe intervention, there is no feasibility or pilot data to support an efficacy trial of daytime only feeding as an intervention that may impact the incidence of delirium. Therefore, a feasibility study is required to generate data with which to inform an efficacy trial.

As covered in the background section, the method in which enteral nutrition is provided to most critically ill patients i.e., continuous enteral feeding (CEF), could be contributing to abnormal circadian rhythms and hence delirium. While there is animal work that supports this hypothesis, it is not known if the provision of enteral nutrition in the daytime only will lead to a

reduction in delirium. If Daytime feeding is effective in reducing the incidence of delirium even a small amount, this will lead to huge benefits to patients, because delirium is so common. Our PPI group tell us that delirium is the most significant concern following survival from critical illness. They are highly supportive of any potential intervention that will reduce the occurrence of delirium. This intervention would be a cheap and rapidly introducible intervention, with effects that patients have told us they want.

3. Assessment and management of risk

Internal risk assessments for the trial will be developed by the trial management team at PenCTU and will be regularly updated throughout the trial. The risk assessment will consider all potential risks associated with the trial which may include trial participants, reliability of the trial results, data confidentiality and trial organisation. The risk assessments will report on the total risk score and category of each risk and any management or mitigation strategies.

This trial does not study the use of a medicinal product, rather the administration method of a known produce, enteral feed, by altering the time frame in which it is given to better match usual human physiology.

The intervention has no known evidence of harm[16]. A scoping review found 14 randomised controlled trials, that included 868 participants, published between 1989 and 2023, where enteral nutrition was withheld for 6 to 12 hours overnight.[16] The patient cohorts were from general or mixed intensive cares, neurosurgical groups and paediatric groups. In these trials, feed was either administered in by bolus, in cyclic patterns or continuously. The overnight fasting times ranged from 6 to 12 hours, with reported primary outcomes of feed intolerance, nutritional delivery, ketosis, gastric pH, ventilator associated pneumonia and circadian rhythms. Significant findings associated with daytime only feeding were increased ketosis and lower gastric acidity. While some of these studies were underpowered to draw conclusions over clinically important outcomes, there is no clear signal of harm from this intervention.

3.1 Evidence relating to specific risk

Feed intolerance.

Overall, the heterogeneity of the definitions used to define feed intolerance prevents conclusive comparison across the published studies. However, no clear signal that daytime only feeding increases feed intolerance was found[16].

Patients who are mechanically ventilated and nursed in the prone position will be excluded or withdrawn from the trial. Prone position nursing is used in the context of hypoxaemic respiratory failure and is a recognised intervention to improve hypoxaemia. However, there are no data concerning the assessment of feed intolerance in this scenario; specifically, how the assessment of gastric residual volumes correlates with feed intolerance when positioned prone. Therefore, for safety reasons, we will exclude or withdraw recruited patients if they are nursed in the prone position.

Reaching nutritional targets

One study found no difference in achieving >60% of the prescribed calorific intake in a group of 41 patients[19]. Continuously fed patients were significantly more likely to achieve >80% of their target nutrition in a cohort of 99 patients[24]. A feasibility trial of 140 critically ill children showed the nutritional intake was lower in the intermittently fed group than in the continuously fed group for the first four days, although this was not associated with an increase in feeding intolerance. [23]. The authors consider that feed delivery was principally limited by feed prescription and feed interruptions.

We have chosen the intervention of allowing catch-up feeding within the daytime, to compensate for time spent with no feed due to procedures. This is a technique used in some ICUs which allows the safe provision of extra enteral nutrition over a fixed time, and it has been added to this trial to minimise the risk of under-feeding.

Metabolic outcomes

In an RCT of 62 patients with a 12 hour continuous vs 12 hours of feed in the daytime, the average glucose measurement was not higher in either group, but there was more hyperglycaemia in the continuously fed group[35]. In a paediatric study, of 140 children fasted for 8-12 hours, there were no severe hypoglycaemic events and there was no difference in the rate of hypo- or hyperglycaemic events between the groups. In this study, neonates e.g. aged <12 months, received supplementary glucose infusions at night[23]. In the same study, ketone levels were significantly higher (median 0.4 (0.2; 1.0) vs. 0.3 (0.1; 0.7) mmol/L, $p < 0.001$) in the fasted group. In the only study that measured respiratory quotient, no difference was foud between the continuously fed and night time fasted group there was a significantly higher level of ketosis ($p=0.001$) in the fasted group[23]. No significant difference in respiratory quotient was found in the single study that measured this[28].

These outcomes favour the DAYDREAM trial intervention over control in terms of risk.

Gastric pH and pneumonia

Both studies that measured gastric pH found a significant decrease in pH in the fasted group[25,26]. The incidence of VAP was not different but there were more bacteria in the stomachs of those with VAP in the continuously fed group[26]

Gastric residual volume (GRV)

For acute admissions to the ICU who are critically ill, the ability to check the gastric residual volume in the assessment of feed intolerance is a component of recommended practice (ESPEN). In acute critical illness, changes in gut function may occur, and so it is desirable to be able to assess the GRV to assess for clinical changes until a state of stability is reached, for example, during recovery and weaning from the ventilator.

Jejunal or post-pyloric feeding is a method that is used in those who have an indication for this such as long-term enteral feeding, are established on feed, and do not have feed intolerance.

It is not possible to assess the GRV with post-pyloric fed patients and so they are excluded from this study.

3.2 Other study risks

There is a moderate risk that the required sample size of 40 participants will not be recruited during the allocated period. The potential reasons for this, along with the mitigation plan are documented in the trial-specific risk assessment. The mitigation plan includes the ongoing monitoring of recruitment by the trial oversight committees.

Risks associated with data protection, including data breaches and data loss, will be mitigated by ensuring all staff who are delegated to conduct study procedures are appropriately qualified and trained. The data capture eCRF (REDCap) also has systems in place to reduce the risk of data breaches [36,37]

Risks associated with the general conduct of the study, including non-compliance with the protocol will be reported via a trial-specific *non-compliance log* and reviewed on an ongoing basis by the Trial Management Group - in order to identify causes and trends, and prevent recurrences.

As the trial is *open label*, there are no risks which could be directly related to the blinding of treatment allocation.

This trial is categorised as Type A (No higher than the risk of standard medical care).

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

In the future definitive trial, the primary research question will be: In mechanically ventilated and enterally fed critically ill adults, will DoF reduce the incidence of delirium during critical illness in the ICU compared to continuous feeding?

Population	Mechanically ventilated and enterally fed critically ill adult patients
Intervention	Enteral feed provided in the daytime only for 14 hours (standard nutritional goals) in ICU (for up to 30 days maximum)
Comparison	Enteral nutrition provided continuously over 24 hours (standard nutritional goals) [usual care] in ICU (for up to 30 days maximum)
Outcome	To support maintenance of a normal circadian pattern and so reduce the incidence of delirium

At this point, we are unable to design the definitive RCT with confidence due to uncertainties around trial processes including recruitment, retention, and data collection. The aim is to conduct a feasibility randomised controlled trial to obtain the data and experience necessary to inform the conduct of the definitive study.

4.1 Primary objective

To conduct a randomised feasibility study of DoF compared to continuous feeding in critically ill patients who have been admitted to ICU for up to 30 days post-randomisation (during ICU stay only).

4.1.1 Feasibility study objectives

This study will provide high-quality data to inform a future efficacy / effectiveness trial

Feasibility objectives include:

1. Estimate rates of screening, recruitment and randomisation rates.
2. To ascertain retention and dropout rate (due to treatment and or trial demands).
3. To determine the fidelity of delivering DoF in adult critically ill patients.
4. Ascertain completeness of data collection throughout the trial including 90 days follow-up.
5. Acceptability of outcome measurements (measured by completion rates and qualitative study).
6. Identify intervention and trial barriers and develop methods to overcome these through a qualitative sub-study.

4.2 Secondary objectives

1. Assess for evidence of efficacy by measuring the number of coma and delirium free days on ICU, use of delirium related medication, physical restraints and Deprivation of Liberty Safeguards. (DoLS).
2. To monitor whether there are any additional safety issues when using daytime only feeding compared to 24 hour feeding.
3. To collect data on the long term psychological and functional impact of daytime feeding.
4. To conduct a sub-study to inform more detailed mechanistic work of daytime only feeding in the critically ill (See Sub-study 2)

5. TABULATED SUMMARY OF OBJECTIVES AND OUTCOMES

5.1 Feasibility objectives and outcomes

Table 1. Feasibility Objectives and outcome measurements

Objectives	**Measurements**
Rates of screening, recruitment, and randomisation	Number of patients screened, recruited and randomised (overall and by centre)
Rates of retention and loss to follow-up	Number of patients remaining in the trial for up to 90 days follow-up (or until death) (overall and by centre)
Fidelity of the intervention	Delivery of at least 65% of prescribed feed during set feeding hours (08:00-22:00 for intervention, 07:00-07:00 for control) for at least 80% of days in ICU.

To ascertain acceptability and completeness of data collection	Completeness of data collection addressing primary and secondary outcomes of a future definitive trial
Identify intervention and trial barriers and develop methods to overcome these	Qualitative focus groups / interviews

5.2. Secondary outcomes and data collection

Table 2. Secondary objectives and outcome measurements

Outcome	**Measurement tool or method *****	**Frequency**
Delirium and coma free days on ICU	Richmond Agitation Scale (RASS) (to demonstrate coma) *Part of Delirium Assessment*	Measure a minimum of 12-hourly and record for each 07.00 - 07.00 24-hour time period
	Confusion Assessment Method for ICU (CAM-ICU) (primary delirium assessment) *Part of Delirium Assessment*	Assess a minimum of every 12 hours if RASS is ≥- 3. (which means not in a coma) record summary for 24 hours 07.00 - 07.00 time period.
	Intensive Care Psychological Assessment Tool (IPAT) (additional delirium assessment) *Part of Delirium Assessment*	Perform data collection if CAM-ICU is negative maximum 24 hourly
	Data from the prescription chart to assess if delirium related drugs have been administered to the participant. (additional delirium assessment)	Daily **
	Use of physical restraints and Deprivation of Liberty Safeguards authorisation (DoLS) (additional delirium evidence)	Daily **

- Richmond Agitation Scale (RASS) – a validated tool for assessing the level of sedation or agitation[38], where a RASS of ≥ 3 means no coma and a CAM-ICU assessment may be performed.
- Confusion Assessment Method for ICU (CAM-ICU) – a validated tool for the diagnosis of delirium in critically ill patients[39] where a positive CAM-ICU means delirium is present.
- Intensive Care Psychological Assessment Tool (IPAT)[40]– a validated tool used to screen for acute distress in ICU patients. Question 8 indicates the presence or absence of hallucinations, and this information is added to the clinical assessment and diagnosis of delirium.
- Acute medications to assess if the patient has received any drug specifically for acute agitated delirium, either as treatment or 'pre-emptive' delivered doses (haloperidol, olanzapine, quetiapine, clonidine, dexmedetomidine)
- Authorisation of Deprivation of Liberty Safeguards (DoLS) as per the Hospital Trusts policy in accordance with the Mental Health Act 2007 and Mental Capacity Act 2005. Restraint - Restraint is an intervention that prevents a person from behaving in ways that threaten to cause harm to themselves, to others, or to hospital property and/or equipment.

Standard delirium assessment is with RASS and CAM-ICU, and an enhanced delirium assessment including all of the above measures will also be used in DAYDREAM. Delirium free days will be calculated using both the standard and enhanced methods. Presence or absence of delirium to be documented at least every 12 hours. If there is delirium documented within a certain day, that is a delirium day. A day is defined as between 07:00 and 07:00 hours as per electronic patient record.

Incidence of feed intolerance	Worsening gastrointestinal function with raised gastric residual volumes (GRV), or a failure to reach nutritional targets and gastrointestinal symptoms in response to feeding attempts[17]	Captured as adverse event of special interest see Section 14.
	Prokinetic drugs administered as per feeding guide based on ESPEN guide	Daily *

Gastric or feeding intolerance is defined by European Society for Clinical Nutrition and Metabolism (ESPEN) international guidance as; worsening gastrointestinal function with raised gastric residual volumes (GRV), **or** a failure to reach nutritional targets, and gastrointestinal symptoms in response to feeding attempts[17]. The incidence of feed intolerance is defined as the number of days in which gastric or feeding intolerance occurs.

Prokinetic drugs: Metoclopramide and Erythromycin		
Incidence of hypoglycaemic events	Glucose < 4.0 mmol/L	Captured as adverse event of special interest see Section 14
Daily incidence of serum glucose < 4.0 mmol/L and interventions used to treat hypoglycaemia, which are recommended to match the local and international guidance on glucose management in the critically ill. The frequency of glucose measurement for each participant per 12-hour time period. The incidence of hypoglycaemic events is defined as the number of days in which there was an episode of glucose <4.0 mmol/L or interventions are used to treat hypoglycaemia. If interventions were used, then data will be captured on the type(s) of treatment administered.		
Long-term psychological and functional impact	EQ-5D-5L (Proxy Version 1 may be used) PTSS-14	90 days post-recruitment via email, post, or phone call from ICU research nurse.
• EQ-5D-5L (Proxy Version 1 may be used) – a validated, health-related, quality of life questionnaire, which has established use with the local psychology follow-up team[40]. The measure asks participants to rate the presence of problems across five domains (Mobility, Self-care, Usual Activities, Pain or Discomfort, Anxiety or Depression) on a five-point scale (where 1 = No problems in the described domain and 5 = extreme problems in the described domain or an inability to complete the described domain). In addition, a visual analogue scale is provided for the informant to rate their current health on a scale from 0–100 (where 100 represents the best health possible). • Post Traumatic Stress Syndrome 14 Questions Inventory (PTSS-14) –a validated tool used to screen for PTSD after ICU discharge. [41] The EQ-5D-5L and the PTSS-14, which will both be done at 90 days as an online form, phone interview or postal form. This is standard practice with the local ICU psychology follow up and will be overseen by the ICU research team.		
Safety	AEs and SAEs	Daily (as required)**
Only Adverse Events and Serious Adverse Events which are considered as related to feeding will be recorded as study data. Section 14 describes the process for reporting AEs and SAEs.		
Mortality	Date of death	Up to 90-days follow-up

*** Taken from electronic patient record**

**** Taken from electronic record and checked with nursing staff**

*** **Training videos of all assessments will be provided.**

6. TRIAL/STUDY TREATMENTS

All patients will be admitted to ICU as per the clinical pathway. All clinical problems will be managed by their usual clinical care teams.

6.1 Intervention arm

Enteral feeding is provided via a naso/orogastric tube continuously over 14 hours (08:00-22:00) and paused between the hours of 22:00 and 08:00 (10 hour overnight fast).

Participants will have their nutritional requirements assessed and prescribed for, as is usual practice in the critically ill. All of the 24-hour feed is to be given over 14 hours between 08:00 to 22:00. The use of catch-up feeding after a pause in feeding during the day is advised for **both** the intervention and control groups. Catch up feeding is permitted between 08:00 and 20:00 in the intervention group. (i.e. up to 2 hours before the end of the feeding period). The feed is stopped at 22:00 and there will be **no** 'maintenance' intravenous fluids given unless there is a separate clinical requirement for this. If the patient is receiving an **insulin infusion** with feeding, then this **must be stopped 30-60 minutes before the feed is stopped** e.g. stopped at 21.30 and blood glucose levels must be monitored a minimum of 2-3 hourly overnight. The blood glucose must be measured between 07:00 and 08:00 so that the use of insulin may be reviewed before recommencing the feed at 08:00 the next day. If the patient has a raised glucose during the nighttime fasting period this should be treated as per normal practice e.g. one glucose over 15 mmol/L or two glucose measurements of over 10 mmol/L indicates commencing an intravenous insulin and dextrose infusion, as is usual care for critical care patients.

The first day in which the intervention is delivered commencing any time between 08.00 and 22.00. It is expected that a full day's nutritional requirement may not be delivered in total on that day due to time constrains and the initial phases of establishing a full feed rate.

- **Choice of Feed**

The choice of feed (type, energy, protein content, etc.) is at the discretion of the treating clinical team and tailored to the individual. Feed types include Osmolite 1.0 kCal/mL, Osmolite 1.2 kCal/mL, Nepro 1.8 kCal/mL and Nutrisan Protein Plus 1.2 kCal/mL and other feeds may be used if indicated. The use of feed with 1.2kCal/mL is encouraged to facilitate adequate nutritional delivery.

Specific clinical circumstances where the choice of feed may be altered are hypernatraemia and renal impairment.

- Hypernatraemia:
    - Osmolyte 1.2 kCal/mL feed with additional NG water administration based on the local hypernatraemia protocol/consultant plan. Alternatively, water added to the feed may be used, dependant on local preferred practice, with the feed rate adjusted as follows -
    - If Na 145-150: Add 250 ml of water to each 500 ml bottle of feed and multiple the feed rate by 1.5. If Na >150: Add 500 ml of water to each 500 ml bottle and

double the feed rate. If total volume per hour exceeds 120 mL consider 3 hourly GRV assessments.

- Renal failure (off renal replacement therapy) – Nepro HP 1.8 kCal/mL only required if patient is at risk of fluid overload, hyperkalaemia or hyperphosphatemia.

For both sites, the local nutrition protocols have been modified to create a study intervention guideline and a control guideline. e.g. translating the study intervention and control into locally accepted patterns of working. The local clinical practice guidelines have been adapted to accurately accommodate the DAYDREAM control and intervention in collaboration with the local clinical teams. This is to enable the local teams to use a nutrition protocol that they are familiar with and to therefore see the study requirements and processes more clearly in terms of their usual practice. The intervention and control protocols for each site are attached as appendix documents, with a generic intervention guideline which describes the intervention without embedding into a local guideline.

6.2 Training for staff

Examples of how to calculate the patients feed rate for the intervention group are provided within the nutrition protocol which details all the clinical practice methods for providing enteral feed, see Feed rate calculations document. Details and examples of catch-up feeding are provided with clinical examples and contact details for real time queries. Educational resources developed in collaboration between LW (dietician), JW (CI) and the local dietetics and education teams will be provided to enable provision of DoF. 'Superusers' (research nurses and education nurses) will be on hand, there is an education video and a 24-hour phone number for advice for local clinical teams delivering the trial.

6.3 Treatment as Usual

Continuous enteral feed (CEF) provided continuously via a naso/orogastric tube over 24 hours as per the local nutrition guidance.

Participants have their nutritional requirements assessed and prescribed for, as is usual practice in the critically ill. The use of catch-up feeding after a pause in feeding is permitted, which is the same for the intervention group. Pauses in feed during the day, for example to facilitate rehabilitation interventions will be timed and recorded, as is the same for the intervention group.

Table 3. Data to collect for feeding details daily

Feeding details (also to be done daily see schedule of events table 4)	For both groups to collect: • Date and time when nasogastric or orogastric feeding tube was confirmed safe to use by a qualified practitioner. • Feed volume and type prescribed 07.00 - 07.00 24 hours period.

	• Feed volume and type delivered 07.00 - 07.00 24 hours period. • Feed volume and type prescribed 08.00 to 22.00. • Feed volume and type delivered 08.00 to 22.00. • Reasons for pauses to feeding. • Energy and protein delivered (derived from volume delivered and feed type).

6.4 Common to *both* intervention and comparator/standard group patients

Procedures:

- The nutritional target for each patient, will be to meet the individual's needs. Feed will be prescribed by the ICU dietician and clinical team as per standard care.
- The choice of feed (type, energy, protein content, etc.) is at the discretion of the treating clinical team and tailored to the individual. Feed types include Osmolite 1.0 kCal/mL, Osmolite 1.2 kCal/mL, Nepro 1.8 kCal/mLand Nutrisan Protein Plus 1.2 kCal/mL and other feeds may be used if indicated. The use of feed with 1.2kCal/mL or more is encouraged to facilitate adequate nutritional delivery.
- The monitoring and management of blood glucose will be as per usual care.
- All critically ill patients are routinely monitored for signs of gastric or feeding intolerance because they are at risk of organ function impairment and failure. It is assessed and treated as per the local and ESPEN guidance and may include the use of metoclopramide and erythromycin (prokinetics). This is detailed in the feeding guides.
- Episodes of hypoglycaemia e.g. blood glucose <4 mmol/L will be monitored for and treated as per national guidance.
- Pauses in feed delivery will be timed and recorded, including the reasons for pauses in feeding.
- The use of catch-up feeding in both groups to compensate for pauses in feeding is permitted and the reasons for its use will be recorded.

6.5 End of intervention

This feeding regime will continue until:

- 30 days after enrolment or discharge from ICU, whichever is sooner
- participant is receiving > 50% of their dietary needs by eating, or
- participant is changed to parenteral nutrition, or

- participant is changed to end of life care, or
- the participant is changed to prone position ventilation.

7. TRIAL DESIGN

DAYDREAM is a multi-centre randomised controlled trial which aims to assess the feasibility of DoF compared to continuous feeding in critically ill patients who have been admitted to ICU (for up to 30 days maximum).

The trial design is summarised in the participant and protocol flow chart (Figure 1).

Enteral feed provided in the daytime only for 14 hours (standard nutritional goals) in ICU (for up to 30 days maximum)
Enteral nutrition provided continuously over 24 hours (standard nutritional goals) [usual care] in ICU (for up to 30 days maximum)

7.1 Trial Setting

The trial will be conducted in two secondary care trusts: University Hospitals Plymouth (UHP) and University Hospital Southampton (UHS). All patients to be cared for in a critical care setting (an ICU), which complies with the Faculty of Intensive Care Medicine (FICM UK) guidance for the provision of intensive care in the UK. Participating units are supported by a principal investigator (PI), research nurses, and dietitians.

There are no other site-specific requirements, but this protocol will consider any differing clinical pathways at each trust.

7.1.1 Target population

Adult patients requiring mechanical ventilation, which is clinically assessed as likely to be for > 24 hours and who are appropriate for enteral feeding. This population has been chosen because ventilated critically ill patients have a high risk for delirium.

7.1.2 Randomisation

Participants will be randomised in a 1:1 ratio to either enteral feed provided in the daytime only for 14 hours or enteral nutrition provided continuously over 24 hours. Randomisation will be stratified by site and PRE-DELIRIC score taken at time of randomisation (> 40% high and very high risk and ≤ 40% low and moderate risk), using a web-based randomisation service provided by the UKCRC-registered Peninsula Clinical Trials Unit (PenCTU) via REDCap.

7.1.3 Blinding

DAYDREAM is an open-label study and as such no investigators, delegated site staff, PenCTU staff, or trial statisticians will be blinded to the participant's treatment/intervention allocation.

8. PARTICIPANT ELIGIBILITY CRITERIA

Forty critically ill adults admitted to an intensive care unit requiring enteral feeding will be recruited. Minimal exclusions are indicated to ensure the generalisability of the results.

8.1 Inclusion criteria

- Adults (aged 18 years and above)
- Unplanned admission to ICU
- Mechanically ventilated, with clinical view it will be for > 24 hours
- Plan to start enteral feeding or enteral feeding has commenced during the daytime only so far
- Likely to require enteral feeding for > 48 hours

8.2 Exclusion criteria

- Planned admissions unless unexpectedly ventilated during first 24 hours of admission.
- Continuous enteral feeding already given overnight (22:00-08:00 hr)
- Known intolerance to enteral feeding or currently unable to absorb enteral feed
- Post-emergency bowel surgery
- Type 1 diabetes or pre-existing insulin therapy (with risk of significant dysglycaemia on fasting for 10 hours)
- Hyponatraemia; serum Na < 115 mmol/L
- Nil-by-mouth
- Clinician considers DoF unsuitable for the patient *and has discussed this with the research team*
- Pregnancy and breast feeding
- Post-pyloric feeding via jejunostomy tube
- Receiving parenteral nutrition
- Dementia, psychosis, bipolar disorder and pre-existing use of antipsychotic drugs (haloperidol, olanzapine, quetiapine) or alcohol use, daily and to excess
- Prone position ventilation; no data to support assessment of GRV in this position

9. TRIAL CONDUCT

Please refer to the schedule of events in Table 4 below for a summary of the study visits and the procedures and data collected at each timepoint.

Table 4. Schedule of Events

Procedures and Data Collection	**Screening**< 24 hours from ICU admission	**Baseline** (Day 0)	**Randomisation** (Day 0)	**Ongoing** whilst ICU inpatient, or up to 30 days	**Circadian** Sub-study (days 3, 4, 5)	**90 days** (+/-7 days) post recruitment
RWPC documented (participant to confirm continued consent when able)	**x**					
Eligibility confirmation	**x**					
Demographics		**x**				
Height (cm)		**x**				
Weight (kg)		**x**		**x**		
PRE-DELIRIC Score*		**x**				
Vital signs (summarised in SOFA scores)*		**x**		**x**		
APACHE II score*		**x**		**x**		
Admission details		**x**				
Comorbidities		**x**				
Regular concomitant medications		**x**		**x**		
Randomisation			**x**			
Intervention delivery			→			
Delirium assessment		**x**		**x**		
Use of delirium drugs (pre-emptive and treatment) and restraints/DoLS		**x**		**x**		
Daily assessment of delivery of steroids e.g. hydrocortisone, dexamethasone, methylprednisolone, prednisolone					**x**	
Hypoglycaemia and glucose management data (glucose tolerance impaired)				**x**		
Feed target delivery volume and time data		**x**		**x**		
Feeding intolerance and prokinetic drugs administered				**x**		
Date and time of extubation and end of mechanical ventilation.				**x**		
Length of stay and mortality data				**x**		**x**

EQ-5D-5L						**x**
PTSS-14						**x**
Adverse event reporting			→			
Circadian sub-study						
Temperature					**x**	
Light and sound exposure (UHP only)					**x**	
Serum cortisol levels					**x**	
Serum mRNA (UHP only)					**x**	

*** PRE-DELIRIC [43] score calculated from age, Urea concentration, APACHE II score, urgency of admission, admission category, RASS score, presence of infection, morphine and sedation. Will be collected at baseline and day 1 only.**

*** Sequential Organ Failure Assessment (SOFA) score is calculated from PaO2, FiO2, mechanical ventilation, platelets, Glasgo coma score, serum bilirubin, mean arterial pressure or vasoactive agents and creatinine or urine output.**

*** Acute Physiology and Chronic Health Evaluation II (APACHE II) score is calculated from; history of immunocompromise, hearth failure class IV, cirrhosis, chronic lung disease or dialysis; age; temperature; mean arterial pressure; pH; heart rate; respiratory rate; sodium; potassium; creatinine; acute renal failure; haematocrit; white blood cell count; Glasgow coma scale; and Fio2.**

9.1 Participant identification and eligibility screening

Site Principal Investigators (PI's) will be responsible for promoting the study amongst relevant staff at their hospitals to optimise participant recruitment. Recruitment performance at each site will be closely monitored by the Trial Management Group (TMG).

All mechanically ventilated adult patients in the ICU will be screened each day for eligibility. The participants will be identified by members of the local intensive care research team with delegated responsibility for screening, including research nurses and clinical staff who may be medically qualified, advanced critical care practitioners or from a nursing background. Eligible patients will then be discussed with their treating ICU physician to confirm agreement with trial enrolment.

Recruitment should be within 24 hours of admission, or if the patient has not received enteral feeding at night and is otherwise eligible, recruitment may occur within 48 hours of admission to ICU. Patients admitted overnight who may be eligible will be identified between 07:30 and 09:00, or throughout the working day by the research team to enable assessment of eligibility and randomisation so that the intervention may be commenced within 08:00 and 22:00 if the patient is randomised to this arm.

All screening data will be recorded by the Principal Investigator (PI) or designee onto the DAYDREAM trial screening log. This data will be recorded on REDCap, to ensure reporting is in line with the consolidated standards of reporting trials (CONSORT) guidelines. Data will be pseudo-anonymised and include the following non-identifiable information: year of birth, sex

at birth, ethnic group, registered to the trial or not, reason if not eligible. Monthly screening log data will be used to monitor trial recruitment and provide feedback to sites.

If a consultee chooses to provide the consent or declaration remotely rather than in-person or over the phone, the completed form will be stored on REDCap. This means that their name and email address (and in the case of a declaration, the consultee's name and email address) will be collected. Participants and consultees will be informed of this in the information sheet.

The outcome of the screening process and reasons for the non-enrolment of potentially eligible patients will be recorded on the DAYDREAM study screening log.

9.2 Recruitment and consent

The research without prior consent (RWPC) model has been chosen for the DAYDREAM trial due to the following reasons

1. The patients are urgent and emergency admissions, and the provision of nutrition is part of the emergency interventions provided to the critically ill.
2. The proposed mechanism by which daytime only feeding would lead to benefits in a reduction in the incidence of delirium depends on circadian rhythms being preserved. This required the feed provision to be only in the day for the whole admission, and it would be prevented if any feed was provided in the nighttime. This means there is a scientific basis for ensuring there is limited delay in providing the intervention in a timely fashion.
3. It is recognised that families and carers of patients on intensive care units experience significant stressors, which lead to more difficulty in considering consent for research studies.
4. The intervention of daytime only feeding is low risk.

RWPC (also known as deferred consent) is well established in ICU practice, making this study practical and fair. Critically ill patients eligible for this study are highly unlikely to have the capacity to consent to research due to sedation and the severity of their illness. Additionally, the severity of their illness causes profound distress to relatives, raising ethical concerns both about the burden of trying to understand the study and the ability of a Personal Consultee (i.e. relative or close friend) to provide an opinion about study participation. For these reasons, attempts to obtain either prior informed consent from the patient, or the prior opinion of a Personal Consultee, are inappropriate.

This method is recommended in the revised declaration of Helsinki (2024). In addition, the urgent nature of treatments delivered in ICU means that any delay to commencing treatment could be detrimental to the patient (and to the scientific validity of the trial). Eligible patients will be randomised to receive the assigned treatment as soon as possible (and no later than 12 hours after fulfilling the eligibility criteria).

9.2.1 Personal Consultee Opinion

Consent will be obtained from patients once they have stabilised and are deemed to have capacity. In the interim, once notified of the enrolment of a patient into the DAYDREAM trial, a delegated member of the site research team will approach the Personal Consultee (in person, via telephone, or via electronic consent [eConsent]) as soon as appropriate and practically possible to discuss the trial and seek their opinion as to the patients' likely wishes and feelings regarding participating in the trial. Ideally, this approach would take place within 24 - 48 hours of randomisation, but once the patient's medical situation is no longer an emergency

A personal consultee is someone whom the person who lacks capacity would trust with important decisions about their welfare but is not acting in a professional or paid capacity. These could include a close relative or friend, carer (unpaid), an individual with Lasting Power of Attorney, or a court-appointed deputy.

Where approached in person, the Personal Consultee will be provided with a Personal Consultee information sheet, containing all the information provided on the PIS, supplemented with information on why the Personal Consultee has been approached at this stage. The PIS will provide information about the background/rationale for the trial, what participation means for the patient (e.g. data collection, follow-up questionnaires), confidentiality and data protection and the future availability of the trial results. Personal Consultees will be given time to read the Personal Consultee information sheet and have an opportunity to ask any questions they may have about the patients' participation in the DAYDREAM trial. A Personal Consultee opinion form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in the trial.

After verifying that the Personal Consultee information sheet and opinion form are understood, the person seeking opinion will invite the Personal Consultee to sign the opinion form and will then add their own name and countersign it. A copy will be given to the Personal Consultee; a copy placed in the patient's medical notes and the original kept in the investigator site file.

If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in the trial, then the trial treatment will be stopped (if ongoing) and the Personal Consultee asked whether, in their opinion, the patient would be willing to continue with ongoing data collection.

Where a Personal Consultee is unable to visit the patient in hospital (e.g. due to infection control measures), this consultation may take place over the telephone. The consultation should be conducted by an experienced member of the site research team with knowledge of intensive care, see Section 9.2.4.

Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 9.2.3). The patient's decision will be final, and will supersede the Personal Consultee, where there is disagreement.

9.2.2 Nominated Consultee Opinion

A Nominated Consultee will be approached in the rare situations where no Personal Consultee is available (or one is available but does not wish to be consulted). They may include an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust or an independent doctor (i.e. not involved in the trial). The process can take place face-to-face (the same process as described in Section 9.2.1), Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 9.2.3). The patient's decision will be final, and will supersede the Nominated Consultee, where there is disagreement.

9.2.3 Patient informed deferred consent

Following randomisation and regaining capacity, patients deemed to have full capacity to provide informed deferred consent will be approached by the PI or a delegated member of the site research team. It is anticipated that this first approach will occur within 24-48 hours of regaining capacity. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in DAYDREAM.

A consent form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence. In the situation where a patient is approached in hospital but wishes to have more time to consider participation, they can request to be approached remotely via the method detailed in section 9.2.4.

The process may take place on ICU, the ward, or when patients have returned home before their 90-day follow-up call. Therefore, it may be face-to-face or alternatively may be undertaken remotely (either electronically or via the telephone).

9.2.4 Remote and Telephone Consent

Since this is a low-risk, non-Clinical Trials of Investigational Medicinal Products (CTIMP) study with risks no higher than that of standard medical care, and in accordance with the Health Research Authority (HRA) and MHRA joint statement on electronic consent methods published on 24th September 2018, remote declarations may be documented utilising an e-consent mechanism *via* REDCap.

The trial should initially be introduced to the consultee over the phone by a clinical staff member and if they are happy to receive further information, the recruitment pack sent via email or in the post, depending on their preference. After the consultee has been given sufficient time after receiving the recruitment pack (at least 24 hours), the research team should contact the consultee at which point they will be given the opportunity to understand the nature, objectives, significance and risks of the trial, and will be encouraged to ask any questions they have, so that they can make an informed decision about whether to provide advice that the patient would want to take part. The declaration form will be presented in an electronic format and declaration will be recorded using a tick box for each clause, a typed name, and confirmation of the declaration. There will be no follow-up with a paper (wet ink)

declaration form, as the electronic signature constitutes documented informed advice. A copy of the eDeclaration form will be made available to the consultee.

Remote consent can also take place with participants with deferred consent who have returned home after being provided with the recruitment pack, see Section 9.2.5.

For patients/consultees who do not wish to provide the consent or declaration electronically (i.e., due to technological difficulties), consent or declarations can also be provided over the telephone. If the consent/declaration is received *via* telephone, the research team member will complete the telephone consent/declaration form, with permission, on the participant's or consultee's behalf. A copy of the form will be sent *via* the post.

If consent/declaration is received via the telephone, the person receiving the consent/declaration will use the telephone consent/declaration forms and will initial next to each clause indicating that the consultee/participant has verbally understood and agreed to each point. The person receiving the telephone consent/declaration must sign the form to confirm that the consultee/participant has understood the information sheet and verbally agreed to the consent clauses.

The research team will follow a study-specific work instruction with details on how to receive consent in-person, via telephone or remotely.

9.2.5 Discharge prior to consent/opinion being confirmed

In the situation where the patient is discharged from hospital with mental capacity prior to confirming their consent decision, an experienced member of the site research team with knowledge of intensive care will attempt a phone call to the patient within 14 working days of the DAYDREAM trial ultimate hospital discharge to: inform them of their involvement in DAYDREAM; provide information about the trial; and seek their consent. The patient information sheet may be sent to the patient by email or by post. The outcome of the telephone call will be documented and signed by person seeking consent on the telephone consent form.

If there is no response to at least three telephone call attempts, or, where no telephone number for the patient is documented, then the patient will be notified of their participation by post. The patient will be sent a patient notification letter, personalised by the most appropriate clinical/research team member, and a copy of the PIS. The letter will direct the patient to the PIS for detailed information on the trial and provide contact details for if the patient wishes to discuss the trial further or to opt-out. In addition, the letter will confirm that the participant's data will be included in the trial unless they notify the site research team otherwise.

Both methods described above will provide patients with the opportunity to opt-out of ongoing data collection or follow-up questionnaires. A decision to opt-out during the telephone call will be documented by the person seeking consent on the telephone consent form. For the postal approach, the patient can actively opt-out by using the telephone contact details provided on the PIS, at any point during the trial.

9.2.6 Refusal or withdrawals of consent/opinion

If a patient declines to provide deferred consent, or a consultee advises that they believe the patient would not choose to participate in the trial, and, if a patient or their Consultee (Personal or Nominated) withdraws consent/opinion at any time during the trial - this decision will be respected and will be abided by. All data up to the point of this decision will be retained in the trial, unless the patient or consultee requests otherwise.

9.2.7 Death prior to consent/opinion being confirmed

If a participant is commenced on the trial and dies prior to the Nominated Consultee being informed of their involvement and the death is unrelated to participation they will not be informed. This is in accordance with previous studies and PPI advice as the relatives and friends will be already upset and do not need the additional information which may cause unneeded stress at this time.

9.3 Baseline data

The research team will be responsible for collecting and recording data in REDCap. To characterise the participant population and summarise balance at baseline across the trial arms the following data will be collected and entered onto the database. Inclusion into DAYDREAM is within 48 hours of admission and baseline data is collected at recruitment into the study.

Table 5. Baseline data collection

Characteristics	**Data collected**
Demographics	Age (years) at baseline and year of birth *
	Sex at birth / self-identified gender
	Ethnic group
Clinical and physical characteristics	Weight (part of feed prescription calculation) (kg)
	Height (cm)
	PRE-DELIRIC score at the time of randomisation
	Urea concentration (highest value of serum urea in 24hrs in mmol/L) *
	Vital signs, summarised in SOFA score (see Table 3)
	APACHE II score *
Admission details	Admission diagnoses as per ICNARC criteria.

	Category of admission* emergency or urgent admissions are eligible.
	Admission category (surgery, medical, trauma, neurology / neurosurgery) *
	When invasive mechanical ventilation was commenced, date and time
	Indication for mechanical ventilation
	Coma (RASS -4/-5 for longer than 8 hours) *
Other clinical problems	Infection (proven or strong suspicion and antibiotics started) *
	Metabolic acidosis (pH < 7.35 with bicarbonate < 24 mmol/L) *
ICU Medication (also to be done daily see schedule of events table)	To include Morphine (mg total in 24 hours) * fentanyl, alfentanil, remifentanil and other opiates. Total dose in 24 hours.
	Sedation (propofol, midazolam, lorazepam) *
	Steroids (hydrocortisone, dexamethasone, methylprednisolone, prednisolone)
	Other regular concomitant medications
Delirium data	Delirium assessment
	Delirium medications
	Restraints/DoLS

*** recorded to be able to input into the Delirium (PRE-DELIRIC) prediction model for intensive care patients, version 2 (recalibrated)**

The PRE-DELIRIC score provides a validated estimate of the risk of delirium for critically ill patients. It includes, APACHE-II score, urea concentration, administered morphine doses in 24 hours, use of sedatives, presence of metabolic acidosis, coma, urgent admission, diagnostic category and presence of infections. The inclusion criteria (critically ill and ventilated) for this study means all patients will be high risk for delirium.

9.4 Randomisation procedure (Day 0)

Following recruitment and completion of the baseline assessments, the patients will be randomised 1:1 to receive DoF or CEF, stratified by site and PRE-DELIRIC score as discussed in Section 7.1.2. An automated confirmation email will be generated when a participant is randomised and sent to the PI and other delegated members of the study team.

Participants allocated to the DoF group should commence feed at 0800, or at any time between 0800 and 2200 hours (i.e. start feeding in the daytime only).

Participants allocated to the CEF group will commence their feed at any time of the day or night as per normal practice, where daily feeding totals are counted from 0700 hrs for each 24-hour period.

9.5 Data collected daily during ICU stay

The study team will be responsible for collecting and recording the outcome data listed in tables 1 and 2 in the trial's REDCap database daily or else otherwise indicated

- Prescribed and delivered feed per day (% of protein and energy target achieved).
- Delirium Assessment (12 hourly)
- PRE-DELIRIC score (Day 1 only)
- ICU medication (including Morphine, fentanyl, alfentanyl, remifentanyl and other opiates and sedation; propofol, midazolam, lorazepam). Total dose in 24 hours
- Daily assessment of delivery of steroids e.g. hydrocortisone, dexamethasone, methylprednisolone, prednisolone.
- Use of physical restraints and DoLS
- Weight.
- Feeding details. Safety events potentially related to feed intolerance:
    - Incidence of feed intolerance (as defined by ESPEN)
    - Incidence of hypoglycaemic events
- Prokinetic drugs administered
- Incidence of hypoglycaemic events
- Date and time of extubation and end of mechanical ventilation (if applicable)

Data collection on ICU to end when trial end of intervention criteria (Section 6.5) are met

9.6 90-day follow-up (+/- 7 days)

Intensive care research nurses will track the journey of participants once they have left ICU. Advice on how to keep in contact with and retain participants will be taken from the PPI group. Outcome measures listed in Table 4 will be collected.

- EQ-5D-5L (Proxy Version 1 may be used)
- PTSS-14
- Mortality
- Length of stay

The patient reported outcome measures will be provided electronically via REDCap. The participants (or consultee) will receive an email with a link to respond. If a participant prefers, they may receive them via the post or completed on the phone, facilitated by the ICU study team.

10. QUALITATIVE SUB-STUDY

The daytime only feeding intervention will be delivered by the clinical critical care team, which includes doctors and nurses of all grades, dieticians, therapies and rehabilitation staff, and advanced critical care practitioners (ACCPs). Their feedback may provide insight into why the intervention may fail or have unexpected consequences. Interviews and focus groups will be led by an experienced qualitative researcher, independent from the intervention team.

10.1 Aim

The aim of the qualitative study is to explore the experiences of the ICU staff delivering the intervention.

10.2 Objectives

- To identify potential barriers to successful delivery of daytime feeding
- To evaluate and modify the educational package used in the future definitive daytime only feeding trial.
- To evaluate the acceptability of collection of data for outcome measures

10.3 Focus groups and semi-structured interviews

The staff who are involved in prescribing and delivering the feed to the participants at UHP will be invited to participate. A flexible approach will be used to organise interviews and focus groups, using the method most appropriate and/or preferred by the individual member of staff. Focus groups will include 3-8 staff of the same role and grade so there is no potential for inhibition of ideas due to perceived hierarchical barriers. Focus groups will be coordinated by a minimum of two researchers per session.

The number of participants will be guided by the concept of information power [44] which incorporates the consideration of:

- the aim of the study, namely the exploration of how critical care staff experience delivering daytime only feeding.
- the sample specificity, recognising there may be some variations within these experiences in relation to different professional roles.
- the use of established theory, because DoF is a novel intervention with limited pre-existing background to draw on.

- quality of dialogue, the researcher will be supported by a medically trained colleague to assist with interview analysis should there be any barriers to understanding.
- analysis strategy, thematic analysis will be employed to explore patterns in the data relevant to the aim of the study.

10.4 Online survey

An option of a survey using the same open questions, will be provided for use by staff at both UHP and SUH. This was a request by stakeholders to open the opportunity for feedback to everyone who could not or did not want to attend an interview or focus group. The content of the online survey will match the topic guide as used in the focus groups.

10.5 Recruitment and Consent

The qualitative sub-study will be promoted in the two units with posters and flyers. In addition, it will be promoted at staff meetings and unit managers will be asked to circulate the flyers to their clinical staff via email.

In UHP the choice of attending a focus group/interview or completing the online survey will be given.

Staff interested in taking part in a focus group or interview will be provided with a participant information sheet and given at least 24 hours to consider taking part. The researcher will answer any questions that they might have concerning the interviews and focus groups. Consent will be provided face to face or via econsent. After consent has been received, a date and time for the interview or focus group will be scheduled.

Staff who want to respond via the online survey will be provided with a link to follow on the flyers.

In SUH staff will be asked if they would complete the online survey only.

10.6 Topic guide

See the qualitative topic guide for the proposed content. Stakeholder activities have been held to develop the guide. These questions have been shared and discussed with several clinical staff from different staff groups to ensure the schedule covers the relevant issues.

In January 2025, an initial stakeholder consultation activity was undertaken to gather initial themes for the qualitative study.

On three occasions in the quite areas close to the clinical environment, the chief investigator spent five minutes with a PowerPoint introducing the study and answering any initial medical questions. She then left the group so the members would feel more able to express their views to the qualitative lead, who is not a regular member of the clinical team or involved in the provision of nutrition or the intervention. Three groups were held ranging in numbers from 5-9 with a total of 19 people involved. The discussions ranged in length from 13 to 20 minutes. The groups included nurses from a range of grades, an ACCP, doctors in training, doctors, a

research nurse, two members of the ICU rehab team, a pharmacist, a dietician and 2 consultants.

The process of recruitment was also discussed with the stakeholder groups The feedback included the suggestion of offering opportunities for both individual semi-structured interviews and focus groups. It was also mentioned that an online option might help with the challenge of catching different shift patters, such as those who only work night shifts. It was suggested that recruitment could be discussed at the daily safety brief and that recruitment posters are put up in the staff and seminar room. Interviews will be held via video conferencing or in person, will be audio recorded, transcribed and checked for accuracy and anonymity. Data from electronic completion of the questions will also be anonymised.

Signposting to Professional Nurse Advocates who are based at UHP ICU will be offered to staff in the event of distress following participation in this qualitative work.

10.7 Analysis

Digitally recorded interview and focus group data will be pseudonymised and transcribed verbatim. The data will be analysed using thematic analysis [45] which involves a process of familiarisation with the data, generating initial codes, identifying potential themes and then reviewing themes.

Researchers will undertake first and second order coding, exploring similarities and differences to develop emergent themes across all data. Researchers will share all emergent themes with participants, to consult on the themes, before final themes are determined.

The thematic analysis will be performed by the local psychology team who have experience in this technique. The findings will inform the next planned phase of this research programme in terms of the staff's experiences of delivering the daytime only feeding intervention and acceptability of the data collection.

10.8 Payment

Staff who take part in the interviews or focus groups will be given a voucher as a thank you for their time.

11. SUB-STUDY 2: CIRCADIAN ANALYSIS

The proposed mechanism by which daytime only feeding may reduce delirium in critically ill patients is based on the hypothesis that feeding throughout the night will disrupt circadian rhythms and reduce the differentiation between day and night. This mechanism is not established in critically ill people. The following sub-study aims to collect preliminary data relating to the assessment of circadian rhythms and their disruption in the critically ill cohort.

11.1 Aims:

1. To assess the feasibility of collecting and interpreting complex circadian data in this critically ill cohort.
2. To understand the advantages and limitations of different circadian biomarkers, and the frequency and precise timing of their measurement, to describe both the circadian rhythms and aspects of rhythm disturbance in the critically ill cohort.
3. To understand the acceptability of collecting and studying these data for patients in critically ill cohort (PPI groups/patient interviews)
4. To gather provisional evidence relating to the proposed mechanism by which the intervention (daytime only feeding) reduces circadian disruption, in comparison to the standard of feeding continuously in the day and overnight.
5. To investigate the influence of other factors that may influence circadian disruption, sleep and delirium in the ICU, such ambient as sound and light conditions.

11.2 Objectives:

1. Measure and describe markers of circadian rhythmicity (circadian biomarkers) in the intervention and control group, including core temperature and circulating cortisol levels.
2. Measure and describe cell-derived markers of circadian rhythmicity (clock gene mRNA) in the intervention and control group in patients at Plymouth.
3. Measure and describe other significant circadian inputs (Zeitgebers) which may interact with both the intervention and outcomes, namely ambient light and sound levels.
4. Assess rates of compliance in collecting these complex data

11.3 Circadian rhythm outcomes

1. Core temperature UHP and SUH
2. Serum cortisol UHP and SUH
3. Circadian mRNA panel (ClinCirc analysis) UHP only, for a maximum of 20 patients.

11.3.1 Characterisation of ambient sound and light levels – UHP site only:

1. Sound

A-weighted sound levels (dBA) will be recorded continuously over 24 hours from a position as close to the patient's ear level as possible and the following calculations performed:

LAeq,T the equivalent continuous sound level integrated over a specified time T: calculated for each hour over the 24-hour period (LAeq1h); over the 24 hours period (LAeq24h), over the daytime period (defined as 0800-2200, LAeq14h) and over the nighttime period (defined as 2200-0800, LAeq10h).
In addition, the counts of individual peaks (the maximum instantaneous fast response sound levels for individual noise events) above pre-defined thresholds of 30, 35, 40, 65 and 80 dbA will be calculated.

2. Light

Illuminance (lux) will be recorded continuously over a 24-hour period from a position as close to the patient's eye level as possible, and subsequent calculations of average light exposures each hour; over 24 hours; over the daytime and nighttime periods (defined as per the study as 08:00-22:00 and 22:00-08:00 respectively) will be performed. The proportion of time where the nocturnal light exposure exceeded predefined thresholds of 5 and 20 lux will also be determined.

11.4 Recruitment and Consent

All enrolled participants who have consented to the sub-study (or where a consultee has indicated they would wish to be included) at both sites will be assessed for eligibility for the circadian sub-study.

11.4.1 Additional exclusion criteria:

1. Unable to access personal or nominated consultee opinion on the patient's inclusion in the circadian sub study prior to 00:00 on day 3 of the study
2. Active temperature management (cooling, warming and targeted temperature management.)
3. Steroid therapy within the previous 24 hours (e.g. dexamethasone, hydrocortisone, methylprednisolone or prednisolone). Patients who are receiving steroids on days 2, 3, 4, and 5 will have cortisol measurements discontinued because these will be uninterpretable and so inappropriate to take samples for during these days.
4. Clinical instability that would preclude any aspect of the circadian assessments.

The reasons for exclusion or discontinuation will be recorded and used in reviewing the overall feasibility of this circadian assessment approach.

11.5 Procedures for data collection

Biomarker collection will occur only on days 3 to 5 of the study. It is proposed that during this time window, circadian patterns, or lack thereof, will be established. The measures to be taken are summarised in Table 6.

11.5.1 Core temperature – both sites

Core temperature (degrees Celsius) will be collected from all enrolled participants, every three hours, from 08:00 on day 3 of the study, to midnight on day 5 of the study. During this period, both temperature and the time of the recording (00:00) will be recorded into REDCap from the electronic patient record where it is routinely recorded by the bedside nurse as part of standard care on the ICU. The standard for temperature measurement in ICU is any of the following; via tympanic/axillary/urinary catheter or rectal temperature probes. Other factors that may influence core temperature, such as the administration of paracetamol within 4 hours prior to the temperature measurement or undergoing renal replacement therapy and targeted temperature management devices, will also be recorded.

Patients receiving targeted temperature management may have temperature measurements recorded but not analysed within the circadian sub study as their temperature will be controlled at a set point for therapeutic reasons. Recording of temperature will be discontinued from the start point of targeted temperature management if it is used.

11.5.2 Serum cortisol – both sites

Serum cortisol will be sampled from all enrolled participants, at both sites, 08:00 on day 3 of the study, to midnight on day 5 of the study, at the following intervals: 08:00; 16:00; 00:00 and 04:00. One test per day can be added onto the routine ICU biochemistry bloods taken at one of these time points, with additional samples being taken at the same time as routine blood gas analysis samples. The total additional blood taken for cortisol levels over 3 days will be approximately 10 ml.

The samples will be collected from indwelling vascular catheters (arterial or central lines) by the study team and analysed centrally at UHP Laboratory. Samples will be centrifuged at 18-25 degrees C, stored at 4 degrees C, and sent via royal mail to be processed at UHP labs as per the laboratory work instruction (developed by UHP laboratory team). Following analysis, all blood samples will be safely destroyed as per standard UHP Laboratory practices.

Blood sampling in ICU patients is routinely performed via a vascular catheter, where repeat blood sampling does not involve additional invasive procedures. Patients who are receiving therapeutic steroids (e.g. dexamethasone, hydrocortisone, methylprednisolone prednisolone) will be not have samples taken and be excluded from the cortisol analysis.

11.5.3. ClinCirc data/clock gene expression (mRNA) - UHP only

Data relating to cellular clock gene expression will be assessed by measuring the serum mRNA levels of a panel of clock genes at 4 hourly intervals permitting serial measurement of circadian biomarkers of interest. [46] Samples will be collected for a 48-hour period, from up to 20 participants at the UHP site only. Blood will be collected from 08:00 on day 3 of the study, at 4 hourly intervals (08:00, 12:00; 16:00; 20:00, 00:00, 04;00), until 04:00 on day 5.

mRNA levels will be analysed using ClinCirc analysis which is an advanced circadian analysis

- Clincirc analysis plan for the mRNA, to be performed by the ClinCirc team in Manchester.

A maximum of 3 mL of blood will be drawn per collection for research purposes. A maximum volume taken over an admission will be 36 mL Samples will pseudo-anonymised at the point

of collection and then transported by designated research staff to the University of Manchester where they will be securely stored, processed, and analysed by delegated study staff. Circadian transcripts (e.g. CLOCK, ARNTL1, PER1, PER2, PER3, CRY1, CRY2, DBP, NPAS2, NR1D1, NR1D2) will be measured using techniques such as RT-qPCR.

Following analysis, all blood samples will be safely destroyed as per standard University of Manchester Laboratory practices.

11.5.4 Ambient sound and light levels - UHP only

To determine the impact of other recognised influences on circadian biomarkers, the ambient light and sound levels to which patients in the circadian sub-study are exposed will also be measured, throughout the time period of circadian data collection, for all participants at the UHP site. Night-time will be defined according to the same criteria as night-time for the study (22:00 to 08:00).

A) Ambient light

Measurement

Ambient light exposure (lux) will be measured at 30 second intervals for a 48-hour period, from 08:00 on day 3 of the study to 08:00 on day 5 of the study, using a datalogging time-synchronised light meter, Extech HD450 (Extech instruments. The light meter will be placed on a small trolley by the head of the bed and mounted to a flexible extension to allow adjustment to match the patients eyeline. The data will be uploaded subsequently to PC via dedicated software and exported as a CSV file. For each participant, the following metrics will be calculated from the raw data using Microsoft Excel:

- Average light exposure (lux) over 24 hours
- Average light exposure (lux) over the daytime period (defined as 08:00-22:00)
- Average light exposure (lux) over the nighttime period (defined as 22:00-08:00)
- Difference between average daytime and nighttime light exposure
- Maximum hourly light exposure (lux) over the 48-hour period
- Average hourly light exposure over the 48-hour period
- The proportion of the nighttime period (22:00 – 08:00) where light exposure exceeds predefined thresholds of 5 lux (based on data demonstrating disruption of melatonin secretion) and 20 lux (based on industrial building standards for new build ICUs)[47]

The proportion of the daytime period where light exposure did *not* reach the predefined thresholds of 100 lux and 1000 lux, based on recommendations by the Health and Safety Executive for general daytime levels on the ward, and for performing clinical tasks, respectively.

Analysis

These values will be used to describe the variation in lighting conditions across the 24-hour period in ICU, which are expected to vary considerably at this latitude across the 12-month period of the study. They will also be used to compare light exposure in control and

intervention groups. Relationships between these values and circadian biomarkers will also be investigated to understand how ambient light may be accounted for in the proposed future efficacy trial.

B) Ambient sound

Measurement

A-weighted sound levels (which reflect how the human ear perceives sound) will be measured at 1 second intervals for a 48-hour period, from 08:00 on day 3 of the study to 08:00 on day 5 of the study, using a datalogging time-synchronised sound level meter (SKU AET-958, ATP instrumentation). The sound meter will be placed on a small trolley by the head of the bed and mounted to a flexible extension to allow adjustment to match the patients earline. The device performs time-averaging between selectable time periods, and will be set to record A-weighted sound levels at 1 second intervals in fast response mode (125 ms) intervals, and the data uploaded to PC via dedicated software and exported as a CSV file. For each participant, the following metrics will be calculated from the raw data using Microsoft Excel:

LAeq,T the equivalent continuous sound level integrated over the following specified time periods, T:

- 1 hour (LAeq1h), for each hour over the 48-hour period
- 24 hours (LAeq24h)
- Daytime period, defined as 08:00-22:00 (LAeq14h)
- Nighttime period, defined as 22:00-08:00 (LAeq10h).

In addition, the counts of individual peaks (LAFmax, the maximum instantaneous fast response sound levels for individual noise events) above pre-defined thresholds of 30, 35, 40, 65 and 80 dbA will be calculated.[48]

Analysis

These values will be used to describe the variation in sound conditions across the 24-hour period in ICU during the study period. They will also be used to compare sound exposure in control and intervention groups. Relationships between these values and circadian biomarkers will also be investigated to understand how ambient light may be accounted for in the proposed future efficacy trial.

Raw logged files and exported Excel files will be stored securely on hospital servers with access restricted to research team. Standard time stamps (BST) will be checked at the time of recording. Data will be cleaned to remove obvious artefacts (such as device disconnection or patient transfer). An event log will be completed at the time of data collection to record the location of the bedspace, and any major events at the bedspace during the period of recording. Statistical analysis of the metrics will be performed using SPSS.

11.6 Circadian data analysis

The circadian biomarkers, temperature and serum circulating cortisol will be analysed for the following features of circadian rhythm and rhythm disruption.

- Cortisol values at each time point across (i.e. 08:00; 17:00; and 04:00 on days 3-5), will be compared between the intervention and control groups
- Cosinor analysis using circadian software (such as CircaCompare) will be used to measure the differential rhythmicity (in both cortisol levels and temperature) between the intervention and control groups. The mesor is the average level of values over 24 h. Amplitude corresponds to the distance between the mesor and the peak of the wave. Acrophase is the phase of the maximal value assumed by the curve.

Table 6. Summary of circadian sub-study analysis

	Days 1&2	**Day 3** (Time zero is 08:00)	**Day 4**	**Day 5**	**Storage temp & location**	**Analysis location**
Cortisol sampling 40 patients, both sites, NIHR funded* Gold top serum gel tube (biochemistry tube)	N/A	08:00 16:00 24:00	04:00 08:00 16:00 24:00	04:00 08:00 16:00 24:00	Storage at 4C to 6C. Store at site until each participant's samples taken and send in a batch. Refer to Standard Operating Procedure doc	UHP Refer to Standard Operating Procedure doc
mRNA sampling max 20 patients at UHP, PMS funded, ClinCirc analysis Tempus™ tubes	N/A	4 hourly: 08:00 12:00 16:00 20:00 24:00	4 hourly: 04:00 08:00 12:00 16:00 20:00 24:00	04:00	Up to 3 days at room temp, then 2 years at -80C	ClinCirc, Manchester, UK
Body temperature 40 patients at UHP, usual care.	N/A	Minimum 3 hourly (Starting 08:00)	Minimum 3 hourly	Minimum 3 hourly	N/A	N/A

Light measurement 10 - 20 patients at UHP	N/A	24-hour average measurement Start 08:00 Number of episodes where the pre-determined threshold is exceeded	24-hour average measurement Start 08:00 Number of episodes where the pre-determined threshold is exceeded	N/A	N/A	N/A
Sound measurement 10 - 20 Patients at UHP	N/A	24-hour average measurement Start 08:00 Number of episodes where the pre-determined threshold is exceeded	24-hour average measurement Start 08:00 Number of episodes where the pre-determined threshold is exceeded	N/A	N/A	N/A

* To be omitted if the patient is prescribed any steroid e.g. dexamethasone, hyrdocotisone, methylprednisolone, prednisolone

NB 24:00 hours is midnight

https://ccforum.biomedcentral.com/articles/10.1186/cc12870 sound levels in 5 UK icus, with average sound and number of peaks over 85dbls. We will use this model.

12. WITHDRAWAL CRITERIA

During the process of obtaining consent/consultee agreement, all participants or consultees will be informed that they are free to withdraw from the study or components of the study e.g., mechanistic sub-study, qualitative interview study, at any point and without any detriment to their care. This will be made clear within the Participant Consent/Consultee declaration form and relevant PIS. If a participant or consultee chooses to withdraw from the study and/or components, their decision will be respectfully accepted. The data collected up until the point of withdrawal will be included in the trial unless otherwise requested by the participant or consultee. Data such as timing and reason for withdrawal (where the participant/consultee provides this) will be collected.

The participants of this study will be emergency admissions to ICU, who are ventilated. They therefore have an expected mortality rate of >20%. If a participant who has been recruited into the DAYDREAM studies dies during their ICU or hospital stay or before the 90 day follow up period, they REMAIN in the trial as is normal practice for ICU studies (See ICNARC).

13. END OF TRIAL

This is defined as the date of the last follow-up visit of the last participant undergoing the study (via telephone or in-person). The sponsor will notify the REC, in writing, within 90 days of the end of the study.

14. SAFETY REPORTING

14.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996):

Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence or effect in a patient participating in a clinical trial, including occurrences which are not necessarily caused by or related to the trial intervention.
Serious Adverse Event (SAE)	An AE is considered serious* if it fulfils one or more of the following criteria: • results in death • is life-threatening** • it prolonged/required hospitalisation • results in persistent/significant disability/incapacity • is a significant or important medical event • is a congenital anomaly • requires medical intervention to prevent one of the above or is otherwise considered medically significant by the investigator (e.g., participant safety is jeopardised). * Serious" and "severe" are not synonymous. “Serious” refers to a specific definition for the outcome of an event (see above), whilst “severe” refers to the intensity of an event (e.g., mild, moderate, severe). For example, it is possible to have a “severe” headache, but the headache itself is not a “serious” event. **The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	An SAE as defined above, which is considered to have been definitely, probably, or possibly caused by either the intervention or the trial procedures and is deemed 'unexpected' - i.e. the reaction is one which has not been foreseen by the CI.

For this trial, only AEs and SAEs considered as related to feeding will be recorded in the trial database. This also includes: Feeding intolerance (multiple occasions) after prokinetics and feed intolerance criteria.

- Aspiration pneumonitis associated with vomiting while receiving enteral feed on ICU.
- Glucose <4 mmol/L despite intervention (hypoglycaemia).
- Glucose tolerance impaired.
- New bowel pathology preventing enteral feeding.
- Gastrointestinal bleeding episodes.

14.2 Operational Definitions

Whilst participants are unlikely to experience harm as direct result of taking part in this trial, processes will be implemented to ensure that any such harms are detected and monitored appropriately. The safety of all participants will be monitored throughout the trial, from Day 0 until the end of the 90-day follow-up. Safety events will be reported in line with the pathway detailed in the following sections.

Given the complexity and severity of illness in the study population, we expect significant numbers of adverse events, serious adverse events and death. It is expected that most of these will be unrelated to the trial because the likelihood of participants being harmed by the DoF intervention or trial procedures is very low. This cohort of patients is expected to have a mortality rate of approximately 15 – 34% based on the ICNARC case ix program and on published data where ventilated patients with no delirium had a 15% observed mortality and those with delirium had 34% observed mortality. [9,49]

As such the PI and site research teams will only report AEs and SAEs related to feeding. AE reporting will follow the HRA guidelines on safety reporting for non-CTIMP studies.

14.2.1 Detecting and recording reportable Adverse Events

The PI/PI delegate is responsible for checking for relevant events throughout the duration of the trial period. Any events meeting the criteria from Day 0 until the end of the 90-day follow-up must be recorded by staff in the participant's health record and in the trial database.

For each AE related to feeding the following information will be collected:

- AE diagnosis/term
- Date and time of AE onset

- Severity of AE
- Outcome of AE

.

14.3 Recording and reporting Serious Adverse Events

Detailed instructions for the recording and reporting of serious adverse events will be provided to sites by the PenCTU in the form of a Work Instruction. The primary means of detecting serious adverse events will be *via* the clinical staff caring for participant.

All SAEs related to feeding up to ICU discharge must be reported by the investigator using the digital PenCTU SAE reporting form within 24 hours of the research team first becoming aware of the event - even if not all information is available at the time. Any change of condition or other follow-up information should be recorded within the eCRF using the PenCTU SAE Update form as soon as possible, and within 24 hours of first awareness. Events will be followed until the event has been resolved, stabilised or to Sponsor satisfaction.

Additionally, the research team should ensure that any (non-elective) hospitalisations or emergency department visits reported by participants at the 90-day follow-up have been reported as serious adverse events, if related to feeding.

For each SAE related to feeding the following information will be collected:

- Full details of the event, including a diagnosis
- MedDRA coding (system organ class and preferred term)
- Duration (start and end dates if applicable)
- Seriousness criteria
- Outcome
- Action taken
- Causality (i.e. if related to DoF intervention/Trial procedures)
- Expectedness (whether event would be considered anticipated)

PenCTU will immediately notify the CI of any reported SAEs at all sites, and the CI will record a second assessment of causal relationship. The CI may upgrade the causality assessment (e.g. from not related to related) but may not downgrade the assessment (e.g. from related to not related). Where a causal relationship to DoF is suggested, the CI will record an assessment of expectedness. Expectedness will be judged on a case-by-case basis. If an event is deemed to be serious, unexpected and related to the intervention (SUSAR) this will be reported to the REC as detailed in Table 7.

14.4 Assessing causality of AEs and SAEs

Causality:

The clinical judgement of a medically qualified doctor (usually the principal investigator or authorised delegate) should be used to determine the causal relationship between AE and the DoF intervention.

- *Not related:* There is no or unlikely evidence of a causal relationship between the event and intervention.
- *Related:* There is evidence that the event is definitely, probably, or possibly related to the intervention.

For participants in the intervention group, the PI will record their opinion on whether the (S)AE was caused by the intervention or by any trial procedures. For participants in the usual care group, the PI will record their opinion on whether the (S)AE was caused by any trial procedures. Causal relationship will be recorded in the participant's record and in the eCRF.

If a doctor is unavailable to assess, initial reports should be submitted to PenCTU without the causality assessment, but they must be followed up with a medical assessment as soon as possible (and within 3 working days of the PI and CI being made aware of the event).

14.4.1 Assessing Expectedness of AEs and SAEs

The assessment of expectedness is only required if the AE or SAE is deemed to be related to the DoF intervention. This assessment is delegated to the Clinical CI who will perform a clinical review.

14.5 Onward reporting of SAEs

Table 7: Onward safety reporting activities and responsibilities

Event	Reported by	Reported to	Reported when	Reported how
Unexpected and related SAEs	Sponsor on behalf of CI	REC† & TSC‡	Within* 15 days	Using non-CTIMP safety report form (available on HRA website), by email.
All reported SAEs	PenCTU	TSC	Quarterly	Line listing, by email
All reported SAEs	PenCTU	Sponsor	Within* 24 hours	Automatically notified via email.

*of the CI becoming aware of the event

†REC - Research Ethics Committee

‡TSC - Trial Steering Committee

14.6 SAE Follow-up Reports

All SAEs should be followed up until clinical recovery is complete or until the participant's status is unlikely to change.

Follow-up reports should be submitted using the eCRF (digital PenCTU SAE reporting form) in any of the following situations:

• Resolution is reached or another change in outcome is confirmed

• Additional information comes to light

• There is an increase in severity

• There is a change to the causality assessment

.

Should additional information come to light, causality should be reassessed and documented as per the sections above. The Seriousness assessment will remain unchanged on follow-up reports as this relates to the point of reporting. Any changes to severity or causality should be recorded and, where there are changes to the causality assessment, consideration should be given to reassessment of expectedness, if relevant.

14.7 Notification of Death

All deaths will be reported to the PenCTU via the eCRF, including those where a medical decision to withdraw care with curative intent has been made.

Note – the term 'Death' alone cannot be reported as an SAE, it must be reported as the outcome of an SAE.

14.8 Coding of adverse events

PenCTU will maintain a register of all recorded adverse events. Events entered into the eCRF will be coded by designated members of PenCTU staff using the Medical Dictionary for Regulatory Activities (MedDRA +version 28.1).). Events will be coded at two levels - the 'preferred term' (PT) and 'System organ class' (SOC). The same version of the MedDRA dictionary will be used throughout the trial.

14.9 Safety oversight

The TMG will discuss any unexpected and related AEs and SAEs and any emerging safety concerns at monthly TMG meetings as required.

Line listings of SAEs, produced by PenCTU, will be reviewed at every TSC meeting in accordance with the details set out in the TSC Charter.

In addition to the above standard safety reporting, we will have a formal review of hypoglycaemic events after 3 patients receiving the intervention have been recruited for each site. This is to have a focused review of glycaemic control during daytime only feeding, the risk of intervention related hypoglycaemia and patient safety as advised by the TSC.

14.10 Pregnancy reporting

If a participant is suspected to be pregnant prior to trial participation (but not aware at time of admission to ICU) the PI or site team must notify the PenCTU within 24 hours of first becoming aware - using the PenCTU electronic pregnancy notification form. If pregnancy is then confirmed during study participation, the participant will be withdrawn from the trial. The Sponsor will be informed of any reported pregnancies by PenCTU within 1 working day of being notified.

15.0 STATISTICS AND DATA ANALYSIS

15.1 Target sample size and justification

Plymouth has 28 critical care beds accommodating general critical care and neurocritical care cases. Southampton general ICU has 22 beds for its general critical care cohort, to be screened for this study.

As a feasibility trial, the key aspect of this study is to inform progression to the main trial. Sample sizes between 24 and 50 have been recommended for feasibility trials [50]. With a sample size of 40 (20 intervention, 20 control), we will be able to estimate a retention rate of 80% to within a 95% confidence interval of +/- 12%.

40 patients are planned across 2 sites. Based on the number of eligible patients from previous ICNARC data for UHP and SUH, and a 10% enrolment rate in 2 sites over 6-9 months 40 is the predicted number of eligible participants. However, a recruitment window of 12 months has been included to allow for error.

15.2 Statistical analysis plan

The trial will be reported in accordance with the CONSORT 2010 statement extension to pilot and feasibility trials [51]. The Statistical Analysis Plan will be signed off by the TMG and TSC prior to database lock.

In brief, descriptive statistics will be reported for the feasibility outcomes: recruitment, retention, and adherence rates (with 95% confidence intervals), quality of data collection, intervention delivery and fidelity. Baseline data and candidate primary and secondary outcomes will be summarised overall and by trial arm. Data will inform a potential definitive study with variability in candidate primary measures calculated and a sample size (power calculation) for the definitive trial estimated for each. Missing data will be described but not imputed. No statistical comparisons between treatment groups will be undertaken on baseline or follow-up data as the trial is not designed to test effectiveness.

Adverse events and serious adverse events will be summarised by preferred term and system organ class by treatment group and grade. Adverse events of special interest (listed in Section 14.1) will be analysed in further detail using a competing risk approach as detailed in SAVVY [52] and events per day in study, as there is a high risk of death as a competing event.

15.3 Summary of baseline data and flow of patients

The analysis and reporting of this feasibility study will follow the CONSORT guidance for pilot and feasibility studies. The flow of participants through the study will be presented in a CONSORT-style diagram with reasons for discontinuation or withdrawal given where available. Descriptive statistics of participants' demographic and baseline characteristics will be presented by allocated groups and overall. No formal between-group comparisons of baseline data will be undertaken. Adverse events will be summarised descriptively.

15.3.1 Progression criteria

RAG stop-go criteria will be used to assess the key feasibility objectives of recruitment and intervention adherence to inform whether a main trial is possible and whether the design or other issues need modification to conduct it successfully. Process data will be used to describe interpreted timelines to identify "fixable", "manageable" and "insurmountable" challenges to site opening, training, data collection and intervention fidelity, regarding both the future main trial and clinical implementation in the event of a positive trial.

We shall progress to a full trial application if minimum success criteria for key feasibility aims/objectives are achieved:

- Proportion of eligible patients recruited (<5%, 5-20%, >20%)
- Fidelity of the intervention (delivery of >65% of the planned feed [53], over no more than 14 hours in 80% of the intervention group)
- Retention of recruited participants (<60%, 60-80%, >80%)
- Completeness of data collection
- Barriers and facilitators to delivering the intervention of daytime only feeding

Table 8. Red, amber, green (RAG) system to guide progression to a definitive trial

	GREEN **Go: proceed with RCT**	**AMBER** **Amend: proceed with changes**	**RED** **Stop: do not proceed unless significant changes are possible**
Proposed recruitment rate %	>20%	5-20%	5%
Retention rate %	>80%	60-80%	<60%

Intervention fidelity %	Delivery of >65% prescribed nutrition, over 14 hours in >80 % of the intervention group	45-65% 60-80%	<45% <60%

15.4 Interim analysis and criteria for the premature termination of the trial

There is no planned interim analysis for this pilot trial.

15.5 Participant analysis population(s)

Primary analysis (in the form of summary statistics, not hypothesis testing/inferential analysis) will be undertaken on an Intention-to-treat (ITT) basis, where participants are analysed according to their allocated group, regardless of adherence to the protocol or lack of participation or completion if allocated to the intervention group.

The safety population will include all participants who consent to participate in the study. Safety data will be collected from the time of commencement of any feed for the control arm patients, and from start of DoF for the intervention arm patients. Collection of safety data will end when a participant completes or withdraws from the study.

15.6 Procedure(s) to account for missing or spurious data

One of the objectives of this pilot trial is to assess the completeness of potential outcome measures for the definitive trial, at the level of both item and outcome measure. Missing outcome data will be noted and used to inform the likely pattern of missing data in a full-scale trial. If a considerable amount of outcome data is missing, this may suggest a need to reconsider the choice of outcome measures and inform the choice of primary outcome measure for any future definitive trial. This may also provide an insight into how missing data can be minimised in any subsequent full-scale trial.

Reasons for being unable to collect data during an assessment will be recorded on the electronic case report form (eCRF), where appropriate. eCRFs will be assessed for missing data by the CTU and sites will be regularly chased for missing data. The CTU will maintain a record of site compliance with eCRF completion. If data completion is poor, a monitoring visit may be scheduled.

The eCRFs will include mandatory fields; if a form is saved without these fields being completed an automatic flag will be displayed to the user. Where questions may need to be left blank, options such as ‘Not applicable’ or ‘Prefer not to say’ will be available, to differentiate these from missing data. Validations will be written into the study database, to raise queries with particular data fields, such as flagging if the date of a visit does not correspond to the correct timepoint. Periodic reminders will be sent out to participants to complete questionnaires, if they have selected to complete these electronically.

PenCTU data manager will write a series of R scripts to perform data tasks to aid data completeness, including checking overall completeness by field of all CRFs, checking all visits

have been recorded in a logical order and checking SAE forms have been completed [54]. The scripts will be run on a weekly basis and any concerns will be raised individually with sites.

15.7 Other statistical considerations.

Statistical analysis will be undertaken once the final group of participants has completed the final assessment at 90 (±14) days post enrolment and the database is locked.

The statistical analyses will be undertaken using R version 4.4.0 or later or StataSE version 18 or later.

16. DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP). The study database will be developed by PenCTU, using the commercial electronic data capture system REDCap.

16.1 Data collection tools

A REDCap database will be used to collect participant screening and outcome data, as well as to record safety events. It will be a web-based, fully validated system, compliant with MHRA guidance and ALCOA+ (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available) principles. Data will be captured in accordance with the best principles of clinical data management and the relevant standard operating procedures on Clinical Data Management System Specification and Validation. PenCTU will be responsible for the database build and system validation. Inbuilt validation features will be utilised alongside post-entry monitoring, performed using validated R scripts to ensure data quality and completeness.

Data will be hosted externally by ARO on Microsoft Azure datacentres located within the UK (Liverpool, England). ARO are NHS DSP Toolkit compliant and hold ISO27001 and Cyber Essentials Plus certifications. Microsoft Azure datacentres' are Service Organisation Control (SOC*) type 1 and 2 compliant. Data will be stored on hardware dedicated to PenCTU's instance of REDCap. All electronic data are regularly backed up and stored with a full audit trail. The electronic data capture forms and configuration of REDCap will be managed by PenCTU's information systems team. Requisite permissions and training required for data collection at any sites will be provided by PenCTU. Data Protection Impact Assessments, Data Sharing Agreements will be developed where appropriate.

16.2 Source data

Source data will include participants' medical records (e.g. for medical history), participant / consultee-completed documents (e.g. informed consent forms, patient-reported outcome measures), paper worksheets provided by PenCTU / electronic data capture forms (eCRFs), laboratory result outputs and data captured in the 24-hour diet recall software. In the context of clinical care, investigator site staff must ensure that details of a patient's participation in the

trial are recorded in the participant's health record. As a minimum, the participant's health record should be updated to include:

- Consent and eligibility for study
- Dates of all study visits and follow ups
- Study related adverse events
- Completion or discontinuation of study

Source data should be compliant with ALCOA+ guidance. The CTU will verify source data and source documents as stipulated in the study monitoring plan. Study data will be recorded on the eCRF or on paper forms which will then be entered into the REDCap eCRF.

Participant questionnaires will be completed on eCRFs. Paper-based options will be available on request and entered onto the eCRFs by site staff.

The investigator should keep a record of all participating patients and all original signed informed consent forms. Any paper forms completed by site staff or participants should be retained in the ISF.

The investigator and trial team will ensure that the participant's identity is protected at every stage of their participation in the trial, according to the Caldicott principles. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

16.3 Access to data

Direct access to investigator site records will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections, in line with participant consent.

16.4 Archiving

Following completion of trial data analysis, the Sponsor will be responsible for archiving the study data and Trial Master File (TMF) in a secure location for at least 5 years after the end of the trial. PenCTU will prepare the TMF for archiving in accordance with the requirements of the Sponsor's SOP. PenCTU will prepare a copy of the final dataset for archiving according to the requirements of the CTU's SOP.

Principal Investigators at sites will be responsible for archiving Investigator Site Files and trial data generated at the site according to local policy. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other trial related information should be labelled, physically or electronically, to ensure retention until the Sponsor gives authorisation to destroy. e.g. "Keep until dd/mm/yyyy" (where the date given is five years after the last participant's final visit).

16.5 Monitoring, Audit and Inspection

In accordance with PenCTU standard operating procedures for risk assessment and monitoring, a specific trial monitoring plan will be generated by the PenCTU, based on the PenCTU's risk assessment, with input from the TMG. The monitoring plan will be signed off by the CI and Sponsor before implementation.

PenCTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance, calendar checks (to identify deviations from participants' visit schedules), consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation logs). Central monitoring will be used to identify areas of potential poor performance at individual investigator sites.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Research Ethics Committee (REC) review & reports

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to International Conference on Harmonisation of Good Practice (GCP) guidelines. All data will be stored securely and help in accordance with the Data Protection Act 2018.

The practices of continuous feeding, catch-up feeding and cyclic feeding (e.g. daytime only) as described in this study are all practiced in critical care or ICU environments.

Conducting research in emergency situations where a patient lacks capacity is regulated by The Medicines for Human Use Act (UK Clinical Trial Regulations) and amendment 2006 which relates to Article 5 from the EU Directive 2001 and HRA Informed Consent Guidance. We have based our assessment of the ethical considerations for this trial on the template outlined at the Health Research Authority Workshop 2012 on conducting emergency research in patients who lack capacity.

Patients enrolled in this trial, due to the nature of their underlying condition, will lack capacity to consent. We will therefore seek informed consent from a personal or professional legal representative, if there is sufficient time available and it is appropriate to do so. If treatment needs to be provided urgently without delay, deferred consent from a personal or professional legal representative using the provisions within the EU Clinical Trials Directive and the Clinical Trials Regulations (2006, No 2984) on the basis that:

- The patient is incapacitated
- Treatment needs to be given urgently
- It is not reasonably practical to obtain consent from a legal representative
- The patients PeaRL will be given information about the trial and given opportunity to say if they believe the patient would object to being included in the trial.
- Consent is sought from the patient as soon as possible after recovery of capacity to make decisions relating to treatment.

- Should the patient subsequently wish to withdraw from the trial at any point, this will be respected.
- The procedure is approved by the Research Ethics Committee.

All correspondence with the REC, including annual reports will be retained in the TMF and ISF. The CI/delegate will notify the REC of the end of the trial. If the trial is ended prematurely, the CI/delegate will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

17.2 Amendments

For any amendments to the trial, the Chief Investigator or designee, in agreement with the Sponsor, will submit the relevant information to the REC and HRA for their review and approval. The Chief Investigator or designee will then work with site teams and R&D departments for them to confirm their continued support for the amended trial.

Substantial amendments will not be implemented before review and acceptance by REC and HRA. The site team/R&D departments have up to 35 days after HRA approval to decide whether they can implement the substantial amendment in practice at sites. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

17.4 Translations

If required, local centres can use hospital interpreter and translator services, if available, to assist with the discussion of the study.

17.5 Protocol compliance

Non-compliances with protocol procedures will be documented and reported on specific *non-compliance* report forms in accordance with PenCTU standard operating procedures.

Protocol non-compliances will be reviewed periodically by the Trial Management Group, with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance will be reviewed by the PenCTU trial manager. PenCTU staff must immediately inform the PenCTU QA Manager if they believe that a serious breach has occurred. Where the trial manager and/or PenCTU QA Manger believes that a non-compliance might constitute a serious breach, the trial manager will ensure that a completed non-compliance report form is provided to the Sponsor immediately.

17.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(1.a) the safety, rights or physical or mental integrity of the participants of the trial;

or

(1.b) the scientific value of the trial

Where a non-compliance meets the above criteria, PenCTU will immediately notify the CI and Sponsor. The Sponsor will email a serious breach report to the REC and to HRA (using the breaches.nres@nhs.net email address) within seven days of becoming aware of the event. email address) within seven days of becoming aware of the event.

18. PUBLIC AND PATIENT INVOLVEMENT

The application for funding for the DAYDREAM trial was developed in partnership with an inclusive PPI group of ICU survivors. PPI groups are held following inclusive invitations to all ICU survivors who were admitted to the ICU for greater than 72 hours. Meetings are held via online meetings. They are facilitated by a trained PPI lead and a specialist ICU clinical psychologist. The trial intervention was discussed, and alterations were made to the terminology used as a result. The intervention was supported by the group. The group are supportive of innovative interventions that may reduce the experience of delirium, which is cited as a significant concern by ICU survivors. The circadian investigations have been discussed with a focus on the volume of blood sampling to be used and this was found to be acceptable. The trial has also been discussed with a Patients Advisory Gorup (PAG) to specifically ask about the consent, the patient information leaflet, dissemination and the follow up questionnaires. The PAG have advised us that email communication is requested in addition to other methods of communication and we have added this to our methods. An ICU survivor has been invited to join the TSC.

We will follow UK standards for public involvement in research in our PPI approach. We will meet with the PPI group at the start of the study and regularly thereafter to enable full involvement through the trial and have included funds to support this. We will work with our PPI group to ensure that we are all clear about expectations and jointly agree a role description, terms of reference and organisational responsibilities including payments. We will provide training and support through informal mentorship with experienced PPI and formal training through our PI group. The group will help keep patients and public informed through the progress of the trial and lead the dissemination of the trial findings to lay persons.

19. DISSEMINATION & OUTPUTS:

The findings of this feasibility study will be made available through several recognised routes and via methods advised by our PPI group. Our local stakeholders request that we present our study, its progress, findings and next steps at the local and regional ICU meetings. Methods of dissemination –

- Publication in a high impact peer reviewed journal, the NIHR Journals Library and where appropriate, publication in health articles of national news outlets.
- Presentation at national and international intensive care research conferences e.g. The State of The Art Intensive Care Society Meeting and the Evidence Based Perioperative Medicine meeting (included in funding application).

Public dissemination though the ICU patient support group, using plain English. Study participants will be able to view the study results on the PenCTU website. They will be sent a link. The PPI lead and CI will ensure personal dissemination to them and provide general anonymised summaries of the findings via social media.

20. ACCESS TO THE FINAL TRIAL DATASET

During the study, the PenCTU data team will have access to the trial dataset, including identifiable participant data. Other members of the CTU and the wider study team will have restricted access to pseudo-anonymised study data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access will be overseen by the CTU data manager and trial manager. Access to the final dataset will be provided to the trial statisticians for analysis.

After the trial has been reported, the anonymised individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g. data dictionaries, blank data collection forms, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requestors whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

21. PAYMENT

No payment for feasibility RCT participants is offered. They will not be asked to travel to the hospital for any extra visits.

Staff who take part in an interview or focus group will be given a voucher worth £25 for their time.

22. DATA PROTECTION AND PATIENT CONFIDENTIALITY

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016. The trial Sponsor is the Data Controller for the trial data. PenCTU is a data processor, centrally managing trial data generated at investigator sites. The University of Plymouth is the data custodian, since data are stored on databases managed by the University of Plymouth.

Data including the number of patients screened, approached and interested in taking part will be collected via a log completed by staff conducting screening. Investigator site staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval. Any paper-based data collection tools (e.g. questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purposed designed data capture systems. Access to the system for all users (including PenCTU staff) is via a secure password-protected web-interface with two-factor authentication. Each participant will be allocated a unique system-generated study number. Participants will be identified in all study-related

documentation by their study number and initials. Data collected and analysed during the study will be pseudonymised by the use of this unique identifier. A record of trial participants' names and contact details, hospital numbers and assigned trial numbers will be stored securely in a locked room at the trial site and is the responsibility of the site PI.

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