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TRAITS Programme: Precision medicine trials for adults treated in critical care units

Submission date 09/02/2023	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 20/09/2023	**Overall study status** Ongoing	
Last Edited 12/12/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
The treatment of critically ill patients represents a significant healthcare burden. Outside of pandemics, almost 1 in 5 patients admitted to ICUs in Scotland die during their hospital stay, and even among survivors to hospital discharge we have shown a 5-year mortality of 23% among ICU survivors. Importantly, patients surviving critical illness have a high prevalence of multimorbidity, and more have socioeconomic deprivation compared to the general Scottish population.
Precision Medicine (PM) refers to treatments that take individual variability into account and matches treatment to individual's illness features. PM is growing in use in cancer care, providing precise treatments for patients based on their genetics. Currently it isn't used in ICU because patients because, unlike cancer patients, they have a rapidly changing illness state. The TRAITS programme aims to enable time-critical precision medicine (TCPM) to be used in critically ill patients.

Who can participate?
Patients aged 16 years or older, receiving organ support in a critical care setting, and resident in Scotland.

What does the study involve?
• We will use routinely collected clinical data to enable efficient design, including linking clinical data from participants to collect trial defined outcomes
• We will collect blood samples to enable identification of treatable trait, changes following treatments and to help identify novel targets for future trials.
• We will run a Scotland-wide platform Randomised Controlled Drug Trial (RCT). Patients will be allocated to usual care only or to a trait linked trial treatment plus usual care.
The RCT will run multiple protocols at the same time, called Trait Specific Protocols (TSPs), which can investigate multiple treatments against pre-defined traits. Our trial design is adaptive which means we can identify new traits, introduce new treatments, and answer questions such as benefit, futility or harm as soon as sufficient data have accrued.
In summary, our clinical trial aims to enable time-critical precision medicine for critically ill patients in Scotland and inform such approaches globally.

TRAITS has 2 stages; (1) the platform and (2) the Trait Specific Protocol (TSP)
The platform requires one blood sample to be taken which will be used to identify a trait. Some baseline data will be collected from medical notes.
In the TSP, participants will be randomised to either IMP and usual care, or usual care.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
Bloods are routinely taken from ICU patients and this is always done by experienced members of the clinical team who are trained to do this. The risk for the platform are therefore very low.
If participants are randomised to receive IMP possible side effects represent a risk to participants and these are listed within the PIL but also discussed as part of the consent discussion. The side effects have been listed as common, rare etc. to help participants interpret this information.

Where is the study run from?
University of Edinburgh and NHS Lothian (ACCORD) (UK)

When is the study starting and how long is it expected to run for?
February 2023 to May 2027

Who is funding the study?
Chief Scientist Office (UK)

Who is the main contact?
Fiona Wee, Senior trial Manager, TRAITS@ed.ac.uk
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Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1006975

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
AC22166, IRAS 1006975, CPMS 58664

Study information

Scientific Title
Evaluation of interventions linked to treatable traits in acute critical illness in adults to enable precision medicine: Data enabled Bayesian adaptive platform randomised clinical trial with embedded biological characterisation (TRAITS Trial)

Acronym
TRAITS

Study objectives
Primary objective:
To evaluate the efficacy of experimental treatments in critically ill adult patients meeting eligibility criteria for a specific treatable trait, compared with usual care, on trial primary outcome of OSFD-21.

Secondary objective:
To evaluate the efficacy of experimental treatments in critically ill adult patients meeting eligibility criteria for a specific treatable trait, compared with usual care, on pre-specified secondary outcomes.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 11/09/2023, Scotland A Research Ethics Committee (South East Scotland Research Ethics Service, 2nd Floor Waverley Gate, 2-4 Waterloo Place , Edinburgh, EH1 3EG, United Kingdom; +44 7814609032; sesres@nhslothian.scot.nhs.uk), ref: 23/SS/0031

Study design
Interventional parallel group randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Critical illness

Interventions
This is a platform trial with multiple arms running within the protocol appendices called Trait Specific Protocols (TSPs). Each TSP recruits different sub set of TRAITS participants and randomises to different interventions.
1. LYMP-RESP TSP. Participants randomised to either Budesonide (1 mg every 12 h for 7 days) and usual care, OR baricitinib (4 mg per day for up to 14 days) and usual care OR usual care
2. ENDO-SHOCK TSP. Participants randomised to either imatinib (800-mg loading dose followed by 400 mg once daily for 9 days) and usual care or usual care.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Budesonide, baricitinib, imatinib

Primary outcome(s)
1. For the overall trial (i.e., referred to as stage-2 evaluation of interventions within each trait), the primary endpoint is number of Organ Support Free Days (OSFD) during the first 21 days from randomisation. This will apply to all treatable traits. Where the participant dies within the first 21 days, the OSFD primary endpoint will be assigned a value of minus 1.
2. For the intermediate adaptive analyses (i.e., stage-1 evaluations of interventions within each treatable trait), the intermediate endpoint will be specific for each treatable trait, and therefore highlighted in trait specific protocols.

Key secondary outcome(s))
Secondary endpoints are those included in the core-outcome set for mechanical ventilation measured using patient records, including:

1. Mortality at different time-points
2. Organ support free days in ICU
3. Days alive outside the hospital (hospital-free days) at 180 days of randomisation
This will apply to all treatable traits.

Additional secondary outcomes may be included in trait-specific protocols.

Completion date
01/05/2027

Eligibility

Key inclusion criteria
Platform inclusion
1. Aged ≥18 years
2. Provision of consent (including deferred consent in accordance with Section 5.2)
3. Receiving organ support in a critical care setting
4. Organ dysfunction of at least one organ (SOFA Score>=2)
5. In clinical team's opinion is likely to require organ support* for ≥24 h post randomisation
6. Resident in Scotland (required for ongoing data linkage)
*Organ support is defined as treatments provided in the critical care units to support one or more of the organ systems, as per the critical care minimum dataset (please see link: https://www.datadictionary.nhs.uk/attributes/organ_system_supported.html). Respiratory support refers to provision of invasive or non-invasive mechanical ventilation, including high-flow nasal cannula with a flow rate ≥30 L per minute and fractional inspired oxygen concentration ≥30%). Cardiovascular support refers to infusion of vasopressor or inotropes. Renal support refers to provision of renal replacement therapy.

Appendix 1: LYMP-RESP TSP inclusion
1. Provision of consent
2. Respiratory dysfunction is defined as PaO2/FiO2 ratio <40 KPa whilst receiving respiratory support with either non-invasive ventilation (including high flow nasal cannula) or invasive mechanical ventilation for 6 hours or longer. Arterial blood gas samples taken within 3 hours of trait eligibility assessment can be used to determine the PaO2/FiO2 criteria.
3. Lymphopenia defined as lymphocyte count <1.2 x 10(9)/L. The lymphocyte count measurements from blood samples done as part of routine clinical care, +/- 36 h of critical care admission could be used. The time window of +/- 36 h reflects the current routine clinical ordering of full blood counts.

Appendix 2: ENDO-SHOCK TSP inclusion
1. Provision of consent
2. Presence of shock: defined as hypotension requiring vasopressor therapy to maintain mean blood pressure 65 mm Hg or greater (equates to cardiovascular SOFA score of 2 or more) and having a blood lactate level greater than 2 mmol/L after adequate initial fluid resuscitation. The term adequate is a clinical judgement. The term initial fluid resuscitation refers to the first set of fluid administration in patients presenting with shock, and acknowledges the fact that resuscitation is an ongoing process. The lactate measurement done as part of routine clinical care using either arterial or venous blood gas, around the time of resuscitation could be used.
3. Evidence of inflammation: defined as C-reactive protein (CRP) 50 mg/L or more OR neutrophil

count >=12 x 10(9)/L. The CRP levels and neutrophil count measurements from blood samples done as part of routine clinical care, around the time of trait eligibility assessment (+/- 36 h window) could be used. The time window of +/- 36 h reflects the current routine clinical care.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Platform exclusion
1. In the Investigator's opinion, the participant is unwilling or unable to comply with the trial intervention and/or procedures
2. Patients was admitted to ICU more than 48 h ago
3. Primary neurological ICU diagnosis
4. Neuromuscular disease and long-term home ventilation
5. Organ transplantation within 90 days
6. Patient not expected to survive 24 hours by the clinician responsible for clinical care
7. Decision to provide only palliative or end-of-life care
8. Prisoners
9. Previous randomisation on the TRAITS trial
10. Individuals with permanent incapacity
11. Known or suspected pregnancy [Note: pregnancy test result is not required for women of childbearing potential (WOCBP) when assessing platform eligibility]
12. Breast feeding

Appendix 1: LYMP-RESP TSP exclusion
Generic
1. Known hypersensitivity to study products or any of its excipients (excipients listed in section 6.1 of the representative SmPC)
2. More than 48 h has elapsed since ICU admission.
3. Patient is known to be pregnant. (A pregnancy test in females with childbearing potential (aged 15-55 years) will be performed prior to enrolment and patients who are pregnant will be excluded.
4. Breastfeeding

Intervention-specific exclusion criteria - Budesonide
5. Patient is already receiving, or a clinical decision has been made to commence inhaled or intravenous corticosteroids

Intervention-specific exclusion criteria – Baricitinib
6. Patients with active TB
7. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product. Diagnosis of sepsis is not a contraindication, given that COVID-19 patients will meet the sepsis case definition.
8. Have received any live vaccine within 4 weeks before screening
9. Alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range
10. Estimated glomerular filtration rate (eGFR) of less than 30 mL/min per 1.73 m^2, immediate need for hemodialysis or hemofiltration;
11. In the opinion of the investigator, unlikely to survive for at least 48 h after screening.
12. Have neutropenia (absolute neutrophil count <1x10(9) cells/L)
13. Have severe lymphopenia (absolute lymphocyte count <0.20x10(9) cells/L)

Appendix 2: ENDO-SHOCK TSP exclusion
Generic
1. Known hypersensitivity to imatinib or any of its excipients (excipients are listed in section 6.1 of the representative Summary Product of Characteristics (SmPC),
2. More than 48 h has elapsed since ICU admission.
3. Patient is known to be pregnant. (A pregnancy test in females with childbearing potential (aged 15-55 years) will be performed prior to enrolment and patients who are pregnant will be excluded.
4. Breastfeeding

Intervention-specific exclusion criteria – Imatinib
5. Patient is already receiving, or a clinical decision has been made to commence imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e. dasatinib, nilotinib, ponatinib)
6. Patient was receiving imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e dasatinib, nilotinib, ponatinib) prior to this hospital admission
7. The treating clinician believes that participation in the domain would not be in the best interests of the patient
8. Severe liver disease or alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) that is more than five times the upper limit of normal or bilirubin more than three times the upper limit of normal
9. Pancytopenia at admission defined as simultaneous presence of lower-than-normal number of red blood cells (haemoglobin less than 135 in men, 125 in women) white blood cells (total counts less than 4 and platelets counts less than 150 in the blood, assessed using a routine blood test.
10. Patients with absolute neutrophil count is less than 1.0x10(9)/l
11. Patients with platelet counts less than 50x10(9)/l
12. Active gastrointestinal bleeding at admission
13. Receiving immune suppressive therapy with a calcineurin inhibitor (e.g. cyclosporine, tacrolimus, everolimus or sirolimus) will exclude a patient from receiving enteral imatinib
14. Patients with long-standing dermatological conditions requiring systemic immunosuppressive medications such as psoriasis, and eczema
15. Patients with known hepatitis B disease
16. Patients on the following drugs: rifampicin, phenytoin, carbamazepine, and dexamethasone.

Date of first enrolment
27/11/2023

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
TRAITS Trial Office
Centre for Inflammation Research (CIR)
The Queen's Medical Research Institute (QMRI)
Edinburgh BioQuarter
The University of Edinburgh
Little France Crescent
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Sponsor information

Organisation
Accord (United Kingdom)

ROR
https://ror.org/01x6s1m65

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office

Alternative Name(s)
CSO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request from TRAITS@ed.ac.uk

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes