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Investigating the effects of intravenous fluids and imatinib in human volunteers with a sepsis-like state

Submission date
12/04/2023

Recruitment status
Recruiting

Registration date
02/04/2024

Overall study status
Ongoing

Last Edited
06/10/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Sepsis is a common, out-of-control immune response to infection, resulting in abnormal blood flow so that some areas may not receive enough blood and oxygen. Sepsis also causes damage to special cells in blood vessels called endothelial cells. The vessels become “leaky”, allowing fluid to move into surrounding areas. This leaked fluid makes it hard for oxygen to reach the cells where it is needed. A key treatment for sepsis is to give fluids intravenously in order to improve blood flow. However, fluid may cause more damage to blood vessels, thereby making swelling worse which makes it even more difficult for oxygen to be delivered where it is required. It is important to establish the effects of fluid on blood vessels and blood flow in sepsis, as it may be either helping or causing harm. It is also important to find out if any drugs can protect blood vessels from damage or control the immune response.

Who can participate?
Adult healthy volunteers

What does the study involve?
Volunteers will receive intravenous lipopolysaccharide (LPS). LPS causes a very mild sepsis-like state for a few hours, similar to mild flu. This will be carried out in a medical research centre. After giving LPS, some volunteers will be given intravenous fluids, and some not. We will perform blood tests to measure the immune response and to assess for blood vessel damage. We will use ultrasound technology to assess for fluid leakage and fluid accumulation.

What are the possible benefits and risks of participating?
1. Complications of LPS therapy: Intravenous LPS will be administered to volunteers whilst they are monitored in the Northern Ireland Clinical Research facility at the Belfast City Hospital. Participants will be observed for 10 hours following LPS administration. Expected symptoms include chills, headache, photophobia (aversion to bright lights), myalgia (muscle aches), arthralgia (joint pains), nausea (feeling sick), and rarely, vomiting. Peak symptom intensity occurs around 1 - 2 hours post-injection, abating to baseline by 6 - 8 hours. Rarely, a volunteer may find the degree of symptoms unacceptable during the height of the response. The symptoms can be

ameliorated with the administration of paracetamol. Other adverse signs include fever, increase or decrease in heart rate and decrease in blood pressure. Medications required to treat adverse effects will be readily available. There are sporadic case reports of participants experiencing bradycardic episodes related to LPS administration. If a participant's heart rate falls below 50 beats per minute or there is concern on the part of the supervising doctor, an appropriate dose of atropine or glycopyrrolate will be administered. Vital signs will be measured at baseline, then every 30 minutes until six hours following LPS administration and then hourly thereafter until participants are allowed home. Participants will be provided with a discharge summary which provides contact details in case of an emergency.

2. Complications of imatinib therapy: Extensive follow-up data of patients with chronic myeloid leukaemia who received imatinib therapy demonstrated that only 4% of patients discontinued imatinib because of adverse events, the overwhelming majority of which were mild. Commonly reported adverse events with chronic use include superficial oedema, muscle cramps, gastrointestinal upset, fatigue and headache. The main adverse events seen with short-term use are gastrointestinal upset: nausea, vomiting and diarrhoea. The single-dosing strategy utilised in this study is extremely unlikely to be problematic.

3. Complications of intravenous fluid therapy: Some participants will receive a total of 30ml/kg Compound Sodium Lactate solution, up to a maximum volume of 2500 ml. This dosing regimen is recommended by the internationally recognised Surviving Sepsis Guidelines for the management of patients with septic shock. There are risks of fluid overload and electrolyte disturbances in participants with impaired renal function, however, in this cohort of healthy volunteers, these risks are minimal. Moreover, previous volunteer studies have verified that this volume of fluid is well tolerated in healthy participants.

4. Complications of cannula insertion and blood sampling: A venous cannula will be inserted into each arm by a trained member of the research team. Intravenous injection of 2ng/kg LPS will be administered via one cannula, whereas the other cannula will facilitate intravenous fluid therapy and blood sampling. Blood sampling can be accompanied by discomfort or by vasovagal symptoms. Risks are minimised through all samples being taken in a fully supported medical facility. Blood will be drawn whilst the volunteer is positioned on a bed or in a self-reclining chair. Volunteers feeling syncopal will be positioned supine and cannulation or venepuncture will be temporarily discontinued. Cannulation and blood sampling will be undertaken by experienced members of the research team. All study personnel will be trained in aseptic techniques for handling peripheral venous lines.

5. Complications of ultrasound imaging: Ultrasonography is a non-invasive method for assessing for the development of fluid leakage in the lungs. Ultrasound assessment will be performed by clinicians who have undergone formal training. Disposable probe covers will be used for each patient and the equipment will be adequately decontaminated as per the manufacturer's instructions. Steps will be taken to ensure participant dignity is maintained throughout the imaging process. Moreover, a chaperone will be present throughout.

Where is the study run from?
Queen's University Belfast Wellcome-Wolfson Institute for Experimental Medicine (Northern Ireland)

When is the study starting and how long is it expected to run for?
August 2022 to July 2026

Who is funding the study?
1. Medical Research Council (UK)
2. British Journal of Anaesthesia (UK)
3. Royal College of Anaesthetists (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1006559

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
22064JS-AS, IRAS 1006559

Study information

Scientific Title
Investigation of novel and established therapies in a human intravenous lipopolysaccharide model of sepsis

Acronym
INITIALISE

Study objectives
Current study objectives as of 18/09/2025:

The main objective of this trial is to assess the effects of intravenous fluid therapy and Imatinib therapy on small blood vessel function in participants with a sepsis like state.

We aim to understand the effects of intravenous fluid therapy and Imatinib therapy on the immune response and on fluid leakage in participants with a sepsis like state.

We also aim to investigate the effects of intravenous fluid therapy alone on small blood vessel function, the immune response and on fluid leakage.

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Previous study objectives:

The main objective of this trial is to assess the effects of intravenous fluid therapy and Imatinib therapy on small blood vessel function in participants with a sepsis like state.

We aim to understand the effects of intravenous fluid therapy and Imatinib therapy on the immune response and on fluid leakage and fluid accumulation in participants with a sepsis like state.

We also aim to investigate the effects of intravenous fluid therapy alone on small blood vessel function, the immune response and on fluid leakage and fluid accumulation.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 09/01/2024, London - Westminster Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)2071048000; westminster.rec@hra.nhs.uk), ref: 23/LO/0394

2. approved 09/01/2024, MHRA (10 South Colonnade, Canary Wharf, London , E14 4PU, United Kingdom; +44 (0)20 3080 6000; info@mhra.gov.uk), ref: 32485/0042/001-0001

Study design

Prospective controlled human experimental study in healthy volunteers using the intravenous lipopolysaccharide (IV LPS) model structured into three linked sub-studies: an exploratory fluid-only group a randomised comparison of IV-LPS with or without fluid resuscitation and a randomised comparison of IV-LPS with or without Imatinib

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Sepsis

Interventions
Current interventions as of 18/09/2025:

Study A (n=5): Healthy volunteers will receive IV Compound Sodium Lactate 30 mL/kg (two 15 mL /kg boluses at 999 mL/h, max 2.5 L) without LPS or Imatinib to assess fluid effects alone.

Study B (n=20): Volunteers will receive IV LPS and be randomised to fluids (30 mL/kg as above) versus no fluids.

Study C (n=16): Volunteers will receive IV LPS and be randomised to oral Imatinib 600 mg (1 h pre-LPS) versus no Imatinib.

Previous Interventions as of 12/08/2024:

This study will assess the biological effects of two interventions on participants receiving intravenous lipopolysaccharide (LPS).

Intervention 1: Start dose of 600mg imatinib administered orally. The administration is to commence 1 hour prior to intravenous LPS.

Intervention 2: 30mls/kg of Compound Sodium Lactate solution (maximum volume of 2500mls) administered in two divided doses (15mls/kg) intravenously. Each bolus will be administered at a fixed rate of 999mls/hr. The administration is to commence 90 minutes following intravenous LPS.

Participants will be randomised into 1 of 4 groups using a Sealed Envelope:
1. LPS only
2. LPS + Compound Sodium Lactate solution
3. LPS + Imatinib
4. LPS + Compound Sodium Lactate solution + Imatinib

Previous interventions:

This study will assess the biological effects of two interventions on participants receiving intravenous lipopolysaccharide (LPS).

Intervention 1: Start dose of 800mg imatinib administered orally. The administration is to commence 1 hour prior to intravenous LPS.

Intervention 2: 30mls/kg of Compound Sodium Lactate solution (maximum volume of 2500mls) administered in two divided doses intravenously over 90 minutes. The administration is to commence 90 minutes following intravenous LPS.

Participants will be randomised into 1 of 4 groups using a Sealed Envelope:
1. LPS only
2. LPS + Compound Sodium Lactate solution
3. LPS + Imatinib
4. LPS + Compound Sodium Lactate solution + Imatinib

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Compound sodium lactate solution, Imatinib

Primary outcome(s)
Current primary outcome measure as of 18/09/2025:

Biomarker based outcomes: Biomarkers of systemic inflammation including but not limited to differential white cell count, C- reactive protein, Il-6 and TNF-α

Biomarkers of endothelial and vascular injury including but not limited to including but not limited to Hyaluronan, Heparan Sulphate and Angiopoietin-2

For Study A, blood sampling and lung ultrasound will be performed at baseline and four subsequent timepoints (T0–T4) aligned with the fluid boluses, but without LPS administration.

For Study B & Study C blood sampling will occur at the following time points:

• T0 (Baseline): Before any intervention.
• T1: 1 h post-LPS.
• T2: 3 h post-LPS
• T3: 5 h post-LPS
• T4: 7 h post-LPS

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Previous primary outcome measures as of 01/10/2024:

1. Inflammation is assessed by measuring circulating levels of white blood cells, C- reactive protein, IL-6 and TNF-α at baseline, 1 hour, 3 hours, 5 hours and 7 hours post intravenous LPS administration

2. Vascular injury is assessed by measuring circulating levels of Hyaluronan, Heparan Sulphate and Angiopoietin-2 at baseline, 1 hour, 3 hours, 5 hours and 7 hours post intravenous LPS administration

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Previous primary outcome measures:

Microvascular flow index (MFI) measured using a CytoCam sublingual microscope at baseline, 90 minutes post-LPS, 2 hours post-LPS, 3 hours post-LPS, 4 hours post-LPS and 8 hours post-LPS.

Key secondary outcome(s))

Current secondary outcome measures as of 18/09/2025:

Ultrasound based outcomes Pulmonary oedema, defined as B-line score

For Study A, blood sampling and lung ultrasound will be performed at baseline and four subsequent timepoints (T0–T4) aligned with the fluid boluses, but without LPS administration.

For Study B & Study C blood sampling will occur at the following time points:

• T0 (Baseline): Before any intervention.
• T1: 1 h post-LPS.
• T2: 3 h post-LPS
• T3: 5 h post-LPS
• T4: 7 h post-LPS

Previous secondary outcome measures as of 01/10/2024:

1. Biological network alteration is assessed by measuring differential mRNA expression at baseline, 1 hour and 5 hours post intravenous LPS administration
2. Pulmonary oedema is assessed by measuring an ultrasound-based B-line score at baseline, 1 hour, 3 hours and 5 hours post intravenous LPS administration
3. Venous congestion is assessed by measuring an ultrasound-based Venous Excess Ultrasound (VExUS) Score at baseline, 1 hour, 3 hours and 5 hours post intravenous LPS administration

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Previous secondary outcome measures:

1. Perfused vessel density measured using a CytoCam sublingual microscope at baseline, 90 minutes post-LPS, 2 hours post-LPS, 3 hours post-LPS, 4 hours post-LPS and 8 hours post-LPS
2. Pulmonary oedema (B line score) measured using an ultrasound device at baseline, 2 hours post-LPS, 3 hours post-LPS and 4 hours post-LPS
3. Systemic venous congestion (VExUS score) measured using an ultrasound device at baseline, 2 hours post-LPS, 3 hours post-LPS and 4 hours post-LPS

Completion date

01/07/2026

Eligibility

Key inclusion criteria
1. Healthy adult volunteers aged between 18 and 40 years of age
2. Informed consent to participate

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
40 years

Sex
All

Key exclusion criteria
1. Current participation in a clinical trial
2. Pregnant or breastfeeding
3. Current history of smoking
4. Alcohol intake > 21 units per week
5. Intake of any prescription and over-the-counter medication (except paracetamol, hormonal contraceptives and hormonal replacement therapy) within 7 days prior to the first dose of IMP
6. Oxygen saturation <95% breathing room air
7. Abnormal findings on history, examination or laboratory tests suggestive of underlying illness (in the opinion of the clinician undertaking screening)
8. History of recurrent vaso-vagal episodes
9. Known history of allergy to imatinib

Date of first enrolment
03/11/2025

Date of final enrolment
31/07/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
Northern Ireland Clinical Research Facility
Belfast City Hospital
Lisburn Road
Belfast
United Kingdom
BT9 7AB

Sponsor information

Organisation
Belfast Health and Social Care Trust

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
British Journal of Anaesthesia

Alternative Name(s)
British Journal of Anaesthesia Ltd, BJA

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Royal College of Anaesthetists

Alternative Name(s)
RCoA Royal College of Anaesthetists, The Royal College of Anaesthetists, RCoA

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

The data we propose to collect will be suitable for sharing as it will be of relevance to other researchers in the fields of sepsis, fluid management and microcirculatory dysfunction. After the publication of our results all data and appropriate metadata will be deposited in the Open Access QUB Research Information Management System, PURE. This can be accessed through the QUB Research Portal. Our paper(s) will contain a clear statement outlining how the primary data can be accessed.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes