Academic and Clinical Central Office for Research and Development

Study Protocol

MIS-ABC Sepsis: Mechanistic Inflammatory Sub-study embedded in the Albumin versus Balanced Crystalloid in Sepsis trial – ABC Sepsis

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CONTENTS

LIST OF ABBREVIATIONS

ABC Sepsis	Albumin versus Balanced Crystalloid Feasibility Study (main randomised control trial)
ACCORD	Academic and Clinical Central Office for Research & Development - Joint Office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigatory Medical Product
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
ED	Emergency Department
EDTA	Ethylenediaminetetraacetic Acid
GCP	Good Clinical Practice
GP	General Practitioner
HDU	High Dependency Unit
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ISF	Investigator Site File
MIS-ABC Sepsis	Mechanistic Inflammatory Sub-study of ABC Sepsis (the sub-study considered in this protocol)
NEWS(2)	National Early Warning Score (2)
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PICC	Peripherally Inserted Central Catheter
PIS	Participant Information Sheet
QA	Quality Assurance
R&D	Research and Development office
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
ST4	Specialty Trainee in 4th year of training

Trial summary

Trial Title	MIS-ABC Sepsis: Mechanistic Inflammatory Sub-study embedded in the Albumin versus Balanced Crystalloid in Sepsis trial – ABC Sepsis
Study Acronym	MIS-ABC Sepsis
Trial Design	Prospective observational study
Trial Participants	Adult patients with community acquired sepsis recruited from the Emergency Department and Medical and Surgical Assessment Units in ~5 UK NHS Hospitals, who are enrolled into the ABC Sepsis trial
Planned Number of Participants	At least 70 participants
Planned Number of Sites	7
Countries Anticipated to be Involved in Trial	UK
Follow up Duration	Sampling period: 24 hours Follow up: 90 days
Total Planned Trial Duration	12 months
Primary Objective	To investigate whether the inflammatory response to community acquired infection/sepsis is dependent on the type of intravenous fluid used during resuscitation.
Primary Endpoint	No primary endpoint: analysis will be exploratory.
Secondary Objectives	1. To understand the inflammatory response in patients with community acquired infection/sepsis by the analysis of a panel of cytokines. 2. To evaluate whether the early inflammatory response to infection/sepsis at the time of presentation to secondary care predicts clinically important outcomes. 3. To investigate whether transcriptomic analysis can provide an explanation for varying physiological response to fluid therapy and clinical outcomes in infection/sepsis.
Secondary Endpoints	No specific secondary endpoints: analysis will be exploratory.
Lay Summary of Trial	This is a sub-study looking to understand how the immune response in patients with infection changes during the early stages of the illness, as well as after intravenous fluid treatment. Participants in the main trial will be given one of two types of fluid (Human Albumin Solution (HAS) and Balanced Crystalloid) via a drip when they present to the hospital with severe infection (sepsis). The main trial is assessing which fluid is better, and we are going to take three blood samples around the time people come to hospital to see what happens to their immune system as a result of the infection and fluid treatment. We hope our findings will explain why one fluid might be better than another. It may also give us an important information about whether we can predict which people might get sicker despite treatment.

1 INTRODUCTION

1.1 BACKGROUND

Systemic illness due to infection is a common reason for patients to present to an Emergency Department (ED) [1]. Up to half develop sepsis [2], defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [3]. Sepsis is a major public health problem with overall mortality estimated at 22%, reflecting a global burden of more than 11 million deaths annually and 52,000 in the UK alone [4,5]. In addition, sepsis is the leading cause of admission to Intensive Care Units (ICU) and the most common cause of ICU death [6], whilst sepsis survivors commonly experience significant morbidity and impaired quality of life [7]. Host response to infection is highly variable, influenced by factors including age, genetics, background physiological status and causative organism. Several distinct sepsis phenotypes have been identified, each with differing patterns of immune response, natural history and clinical outcomes [8]. The balance between the pro- and anti-inflammatory response to infection is crucial to determining clinical course [9].

IV fluids in Sepsis

Patients with sepsis often present with hypotension. This is multifactorial in aetiology but primarily owed to septic shock (due to the systemic effects of endothelial damage, endothelial dysfunction and increased capillary permeability) and hypovolaemia caused by reduced oral intake, increased losses or bleeding during the illness period [10].

This hypotension is addressed, in part, by intravenous fluid therapy. All key national and international guidance advocates fluid resuscitation in septic patients who are hypotensive, although a significant degree of uncertainty exists in the best type of fluid to use, the volume of fluid that should be used and the stage at which fluid is no longer useful for these patients and vasoactive medications must be used. The ABC Sepsis pilot study aims to assess the feasibility of a pragmatic trial comparing two types of intravenous fluid: albumin solution versus balanced crystalloid.

Types of IV fluid

There are two types of commonly used IV fluid in the resuscitative management of patients with Sepsis. These are crystalloid (balanced and unbalance) and large molecule colloid fluids.

Balanced crystalloids contain salts at physiological concentrations found in healthy humans, and are advocated as first line for sepsis by NICE and the surviving sepsis guidelines [11]. Resuscitation with crystalloid (either balanced or unbalanced) is the preferred treatment of choice for shocked septic patients according to an international survey [12].

Albumin, used in this setting as 5% Human Albumin Solution (HAS), is a colloid fluid which NICE directs clinicians to consider for patients with sepsis and shock [13]. However its specific role in sepsis management is, undefined and is largely clinician dependent in the absence of definitive evidence for its use.

The Evidence for Albumin

Albumin is a protein produced by the liver which is responsible for 80% of the intravascular cellular oncotic pressure. Other functions include a pivotal role in acid-base homeostasis, transport of a number of key molecules including drugs, and scavenging of reactive oxygen species [14].

Hypoalbuminaemia in sepsis is a poor prognostic factor for mortality, probably reflecting the severity of disease through endothelial dysfunction and decreased serum albumin half-life [15,16].

A small number of trials have examined the use of albumin in sepsis. The SAFE trial randomised ICU patients to 4% albumin or normal saline for intravascular fluid resuscitation for 28 days, and found no difference between 28-day mortality, and although a pre-specified

subgroup analysis of patients with severe sepsis signalled a benefit for albumin, this too did not reach statistical significance [17]. The ALBIOS study randomised patients with severe sepsis to either 20% albumin and crystalloid fluid or crystalloid fluid alone, with the former arm targeting serum albumin levels of above 30g/L or more. Again, this study found no significant difference between 28 day mortality [18]. However, a subsequent secondary analysis in patients with severe shock and raised lactate identified a survival benefit in the albumin arm reaching statistical significance [19]. A 2014 meta-analysis which included these, amongst three other trials, found a significant improvement in mortality for patients with severe septic shock, and trends towards benefit for those with severe sepsis against crystalloid [20].

These studies have demonstrated safety of albumin but are yet to demonstrate a significant survival benefit in ICU patients. Although undoubtedly these studies select for the sickest patients with sepsis, it is possible that studies in such environments miss a cohort of severely unwell patients who are not suitable for ICU but who may benefit in a similar way from the treatment. Intervention at admission to ICU may even be too late to interrupt the downward-spiralling sequelae of septic shock like end organ failure in some patients.

Immunology and Predicting Response to Treatment

Whilst in broad terms, the rationale for these different intravenous therapies is underpinned by physiological factors, it is highly likely that an individual's immunological response to sepsis and our treatments, will affect this physiology. It may also predict whether and explain why one treatment option is better than another.

The measurement of novel sepsis biomarkers has great potential to fulfil this knowledge gap. Several have already been shown to predict 30-day mortality. However, their ability to predict deterioration when measured at time of hospital presentation is largely unknown. In addition, many promising biomarkers have not been directly evaluated in the relevant population, ED patients with suspected sepsis. We propose to measure pro and anti-inflammatory cytokines (GM-CSF; IFN gamma; IL-1 beta; IL-2; IL-4; IL-5; IL-6; IL-8 (CXCL8); IL-10 (CXCL10); IL-12p70; IL-13; IL-17A (CTLA-8); MCP-3 (CCL7); and TNF alpha). Our rationale is based on the premise that these cytokines are acutely altered in sepsis and may predict different risks (such as clinical severity or risk of deterioration).

Accurate prediction of deterioration prior to the onset of critical illness is key to improving outcomes for patients with sepsis. This enables prompt delivery of treatment "bundles" and consideration of timely ICU admission, both associated with improved survival [21,22]. Currently, patients in the ED with features of systemic infection are risk-stratified using clinical scores and lactate measurement. However, these methods demonstrate inadequate sensitivity and specificity when validated against 30-day clinical outcomes [23], and tell us little about the time-course of deterioration. Consequently, their utility as tools to guide "shop-floor" decision making is questionable. Improved understating of inflammatory cytokine changes during sepsis could aid development of a better tool to differentiate patients at high risk of deterioration. This would substantially inform clinical decisions around escalation of care and the initial level of monitoring required.

We hypothesise that different types of intravenous fluids used in resuscitation (albumin versus balanced crystalloid) may mediate different pro and anti-inflammatory response as measured by these cytokines. We also hypothesise that plasma levels of these cytokines, measured at time of ED admission, will enable improved differentiation of patients with suspected sepsis who are at high risk of deterioration

1.2 RATIONALE FOR STUDY

Currently, there is controversy about the optimal fluid choice in patients presenting to hospital with sepsis. Understanding how each fluid type affects the underlying inflammatory process may provide a mechanistic argument for clinician choice, future research and professional recommendations.

MIS-ABC Sepsis is a sub-study of the ABC-Sepsis trial, a pilot feasibility trial recruiting patients with community acquired infection/sepsis with a NEWS2 score of five or more and randomising the participants to receiving either balanced crystalloid or 5% HAS as the intravenous resuscitation fluid up to six hours after randomisation.

MIS-ABC Sepsis will take serial blood samples from a small number of these participants, at hospital presentation and at two further points early during the patient's admission, to allow analysis of how inflammation changes during their course of illness. Investigating temporal change and differences between treatment arms of the main study will allow a nuanced analysis of the interplay between severity of illness, physiological changes over time and any potential differences between fluid treatment arm.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To investigate whether the inflammatory response to infection/sepsis is dependent on the type of intravenous fluid used during resuscitation in the Emergency Department.

2.1.2 Secondary Objectives

1. To understand the inflammatory response in patients with community acquired infection/sepsis by the analysis of a panel of cytokines.
2. To evaluate whether the early inflammatory response to infection/sepsis at the time of presentation to secondary care predicts clinically important outcomes.
3. To investigate whether transcriptomic analysis can provide an explanation for varying physiological response to fluid therapy and clinical outcomes in infection/sepsis.

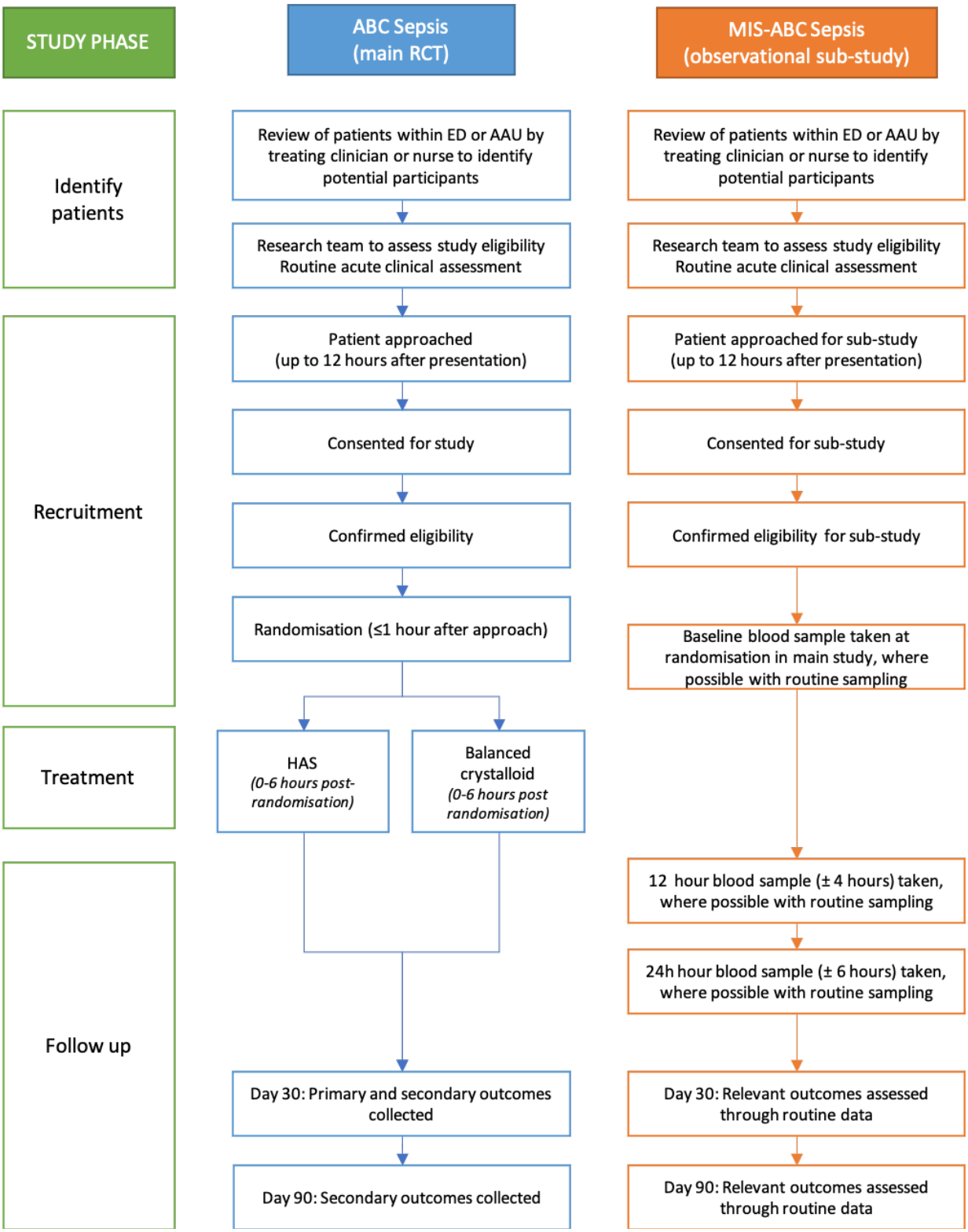
2.2 ENDPOINTS

This study is exploratory in nature and we have not set primary or secondary endpoints. However, prospective planning for analysis has been conducted and is detailed in Section 9.2 Proposed Analysis.

3 STUDY DESIGN

This is a prospective observational study enrolling patients randomised to the ABC Sepsis study. Centres for this trial will be selected from UK NHS hospitals who are recruiting to the main ABC Sepsis study. Participants will be recruited as soon as possible, and up to 12 hours after presentation to the Emergency Department, Surgical Assessment Unit or Medical Admissions Unit.

The treatment phase of the main study spans 6 hours following randomisation, with the follow up period extending to 90 days. This sub-study requires three blood samples: immediately after enrolment, at approximately 12 and 24 hours thereafter. The follow up period similarly extends to 90 days, using routine data from the medical records for follow up.



Study diagram depicting MIS-ABC Sepsis trial in the context of the main ABC Sepsis feasibility trial.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit at least 70 patients from approximately 7 sites, ideally with at least 30 patients from each intervention arm of ABC Sepsis. The main study aims to recruit 300 patients from approximately 15 sites. Site selection for this sub-study will depend on whether that site has capacity to do so and will likely focus on sites who have demonstrated success with recruitment to the main study. Recruitment will take place over a period of around 6 months.

4.2 INCLUSION CRITERIA

1. Able to obtain informed consent
2. Eligible for and randomised into the ABC Sepsis trial

4.3 EXCLUSION CRITERIA

There are no specific exclusion criteria for this sub-study, and therefore it will map directly onto those of the ABC Sepsis trial:

1. Excluded from the ABC Sepsis trial

4.4 CO-ENROLMENT

Co-enrolment is permitted between the ABC Sepsis study and this MIS-ABC Sepsis (observational) study.

Other co-enrolment considerations will follow those of the main study and investigators should refer to the ABC Sepsis protocol before considering co-enrolment. In the case of co-enrolment apart from that of MIS-ABC Sepsis (this sub-study) and ABC Sepsis (main study), the ACCORD policy will be consulted (POL008 Co-enrolment Policy) and relevant forms completed.

Accidental or unintentional co-enrolment will be avoided with thorough consultation of available medical records and routine participant questioning. Should co-enrolment occur accidentally or unintentionally, a protocol deviation will be reported to the Sponsor.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

The research team, where it is locally agreed that they are part of the clinical care team, will identify patients using triage information and clinical or electronic records in the Emergency Department, Medical or Surgical Assessment Units or any other area used for acute assessment in the recruiting site. In this case, it is anticipated they would identify patients and make the first approach. Any member of the clinical team who has received general and trial specific training and is on the delegation log may also identify patients in this way. Where researchers are not considered to be part of the care team, the researcher will ask a member of the direct care team to identify suitable patients and ask permission from the patient to be approached by the researcher to discuss participation. Triage notes or documentation of presenting complaint will also be consulted to see whether approaching participants for the study is appropriate. Patients may be approached for up to 12 hours after presentation for the ABC Sepsis study, so the same timeframe will be applied to this sub study. It is aimed that participant identification, approach, consenting and enrolment will be done simultaneously with

the main trial. It will be made clear at all points that the sub-study is both a separate, but linked, project, and also entirely optional for those participating in ABC Sepsis. Patient information, both written and verbal, will be designed to be complementary to the ABC Sepsis trial, building on information already explained to the potential participant, with an aim to reduce burden.

5.2 CONSENTING PARTICIPANTS

The consent pathway below will be followed to determine the appropriate mechanism of consent to use for an individual participant and details where consent to continue is needed. This mechanism will differ between sites recruiting in England and Scotland.

5.2.1 Participant consent

Potentially eligible participants who are willing to take part in the study, and have capacity to do so, will be asked to provide written informed consent. Consent will be obtained by trained members of the clinical team or members of the research team who have been delegated this responsibility. The Investigator is responsible for the delivery of processes to ensure informed consent is obtained before any protocol specific procedures are carried out. The decision of a patient to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

The participant will be given a Patient Information Sheet (PIS), which will explain the aims of the trial and the potential risks and benefits of the study treatments. The participant will be given enough time to consider the trial and ask questions regarding their participation in the trial. Due to the need to sample at or before the time of the ABC Sepsis treatment starting, there may not be long for the participant to consider the trial. Ideally, a period of 30-40 minutes will be given but it may be only 10-15 minutes due to the need for fluid resuscitation to begin. The research teams are experienced at recruiting patients in the emergency environment and given the nature of the intervention and the burden of the trial we believe this to be reasonable.

Potential participants will receive adequate oral and written information. The oral explanation to the patient will be performed by a member of the research team or a trained and delegated member of the clinical team and must cover all the elements specified in the Participant Information Sheet and Consent Form. The patient must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The patient must be given sufficient time to consider all the information provided. It should be emphasised that the patient may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Consent Form to confirm that consent has been obtained. If the participant is unable to sign the consent form for themselves then the witnessed verbal consent form can be used.

The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant's medical notes.

Capacity will be assessed by the Principal Investigator (PI) or a clinician responsible for the treatment of the participant as part of the ABC Sepsis trial. This assessment of capacity will be documented in the participant's medical records.

5.2.2 Personal Representative consent

If a patient is not considered to have capacity to consent, then a Personal Representative will be approached for consent.

In Scotland this is defined as:

Personal legal representative i.e. Adult's Welfare Guardian or Welfare Attorney, or if not appointed the adult's nearest relative.

In England and Wales this is defined as:

Personal legal representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult and is available and willing to do so.

If a Personal Representative is present, they will be given information about the trial in the Personal Representative Information Sheet. The Personal Representative will be given enough time to consider the trial and ask questions regarding their relative's participation in the trial. Ideally, a period of 30-40 minutes will be given but this may be only 10-15 minutes due to the need the main trial interventions to begin within one hour and the sampling to happen simultaneously.

The Personal Representative will be told they are being asked to give consent on behalf of the incapacitated adult, that they are free to decide whether they wish to make this decision or not and that they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision. They will be informed that their relative will be asked whether or not they wish to continue in the study once they have regained capacity to do so.

If they indicate they have had time to consider the trial, the impact on their relative and have been provided with the answers to any trial related questions, they will be asked to provide written consent. The Investigator or delegated member of the trial team and the Personal Representative will sign and date the Consent Form to confirm that consent has been obtained. The original consent form will be filed in the ISF, the participant will receive a copy of this document and a copy filed in the participant's medical notes.

5.2.3 Consent via Telephone

Every effort will be made to approach and consent the Personal Representative in person. If the Personal Representative is only contactable by telephone then the informed consent process is permitted via telephone or an appropriate video conferencing technology such as NHS near me, provided the following:

- The Representative who is being contacted has previously had the opportunity to discuss the clinical aspects of the patient's care with the clinical team;
- A member of the clinical team has sought permission for the Personal Representative to be contacted by a member of the clinical or research team regarding potential involvement in the study;
- The approach to discuss consent is clearly identified as separate to any discussions made between the representative and the clinical team.

A member of the research team will contact the Personal Representative by telephone/videoconferencing technology to explain what the study entails and answer any questions they may have. The Personal Representative will be given time to read and consider the information sheet. In situations where the Personal Representative does not have a copy of the PIS this will be read to them. Ideally, a period of 30-40 minutes will be given but this may be only 10-15 minutes due to the need for fluid resuscitation to begin within one hour. If the Personal Representative chooses to enrol the patient onto the study, verbal consent will be obtained by a member of the research team who conducted the interview and will sign the consent form. This will be witnessed by an independent member of staff.

In this circumstance, the participant must also receive information, according to their capacity of understanding, about the trial and its risks and benefits.

A copy of the signed Personal Representative Witness consent form will be sent to the Personal Representative electronically or by post along with a Personal Representative PIS and Consent form for signature by the Personal Representative. All efforts will be made to obtain a signature on the Personal Representative Consent form either electronically or by post. However, in the absence of this signature, a consent form completed by a member of the research team and witnessed by an independent member of staff will be acceptable.

If there is no response from the Personal Representative one further reminder can be send after one month. If the Personal Representative does not return the signed consent form but does not ask for the participant to be withdrawn from the trial, the Professional Representative consent will remain valid and the patient will remain in the trial.

If a Personal Representative objects to the inclusion of the patient in the trial their views will be respected and the patient not enrolled into the study.

In sites recruiting in Scotland: If the patient does not have capacity, and there is not a Personal Representative available, the patient will not be enrolled in the MIS-ABC Sepsis sub-study. Notably, this differs from the consent process with the ABC Sepsis study where a Professional Representative may be sought, or deferred consent may be used. The difference between recruitment at sites in England and Scotland within this study, and between this study and ABC Sepsis, is a result of what is permitted for non-CTIMP trials by the Adults With Incapacity (Scotland) Act 2000.

5.2.4 Professional Representative consent (England only)

In sites recruiting in England: If the patient does not have capacity, and there is not a Personal representative available, consent from a Professional Representative will be sought. The definition is as follows:

Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider

If there is not a Personal Representative immediately available (within 30 minutes), a Professional Representative will be approached to determine if it is appropriate for the patient to be entered into the trial so that treatment could be commenced within one hour. A Personal Representative should be approached for consent to continue as soon as they are available, and it is feasible to do so. If the Personal Representative is unable to visit the hospital in person, the consent form will be sent to them by email or post. The Personal Representative will be asked to return the signed consent form if they wish to remain in the trial or contact the study team if they wish to be withdrawn. If the patient does not return the signed consent form but does not ask to be withdrawn from the trial, the Professional Representative consent will remain valid.

5.2.5 Deferred Consent (England only)

Patients who have “life threatening features” and who lack temporary capacity due to their current illness can be recruited to the trial using deferred consent if there is no Personal/Professional Representative to give consent on their behalf within 30 minutes so that treatment can be commenced within one hour. The decision to defer consent should be made by a senior doctor, i.e. ST4 (or above) or consultant, who has appropriate trial training and this should be clearly documented.

The patient would be enrolled into the trial and receive their allocated treatment. Consent would be sought as soon as possible from a Personal Representative (or a Professional Representative if they are available sooner). If a Personal/Professional Representative

declines to give consent for continuation at this stage, their wishes will be respected and the withdrawal process in section 5.4 will be followed.

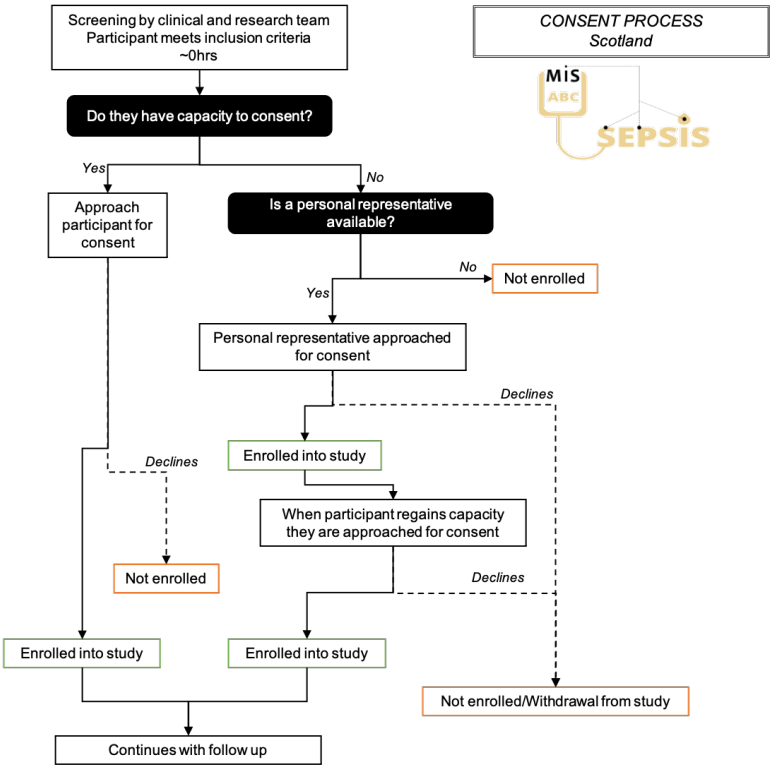
5.2.6 When the participant regains capacity

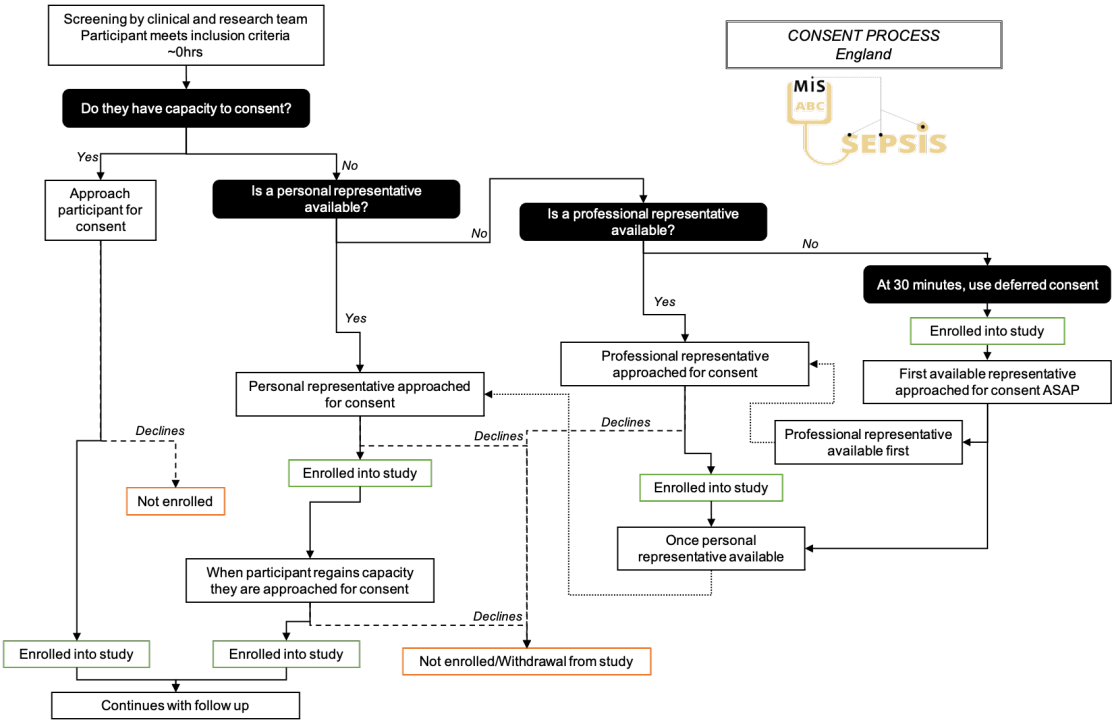
When the participant regains capacity to consent (as assessed by a clinician), they will be given a Recovered Capacity PIS which will explain what has happened to them so far and seek written consent for continued participation in the trial. This will be done as soon as it is feasibly possible. If the participant is happy to continue, they will be asked to provide written consent. The Investigator or delegated member of the trial team and the participant will sign and date the Consent Form to confirm that consent has been obtained. The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant's medical notes.

In the event that a patient is not able to be approached for consent to remain in the trial prior to hospital discharge, the local research team will seek written consent by sending a PIS and consent form by post. The patient will be asked to return the signed consent form if they wish to remain in the trial or contact the study team if they wish to be withdrawn. If there is no response, one further reminder can be sent after one month by post. If the participant does not return the signed consent form but does not ask to be withdrawn from the trial, the Professional Representative consent will remain valid and the participant will remain in the trial.

If the participant is not happy to continue, the withdrawal process in section 5.4 will be followed.

For any participant who was included but does not regain full capacity, consent from the Personal Representative will stand, or from the Professional Representative where there is no Personal Representative. Where no consent is given by any legal representative, i.e. deferred consent is used and no subsequent consent obtained, or a participant dies before any consent obtained the patient data collected would be destroyed. Patients with permanent incapacity will not be recruited and this is an exclusion criterion.


Screening by clinical and research team
Participant meets inclusion criteria
~0hrs
CONSENT PROCESS
Scotland
Do they have capacity to consent?
Yes
No
Approach participant for consent
Is a personal representative available?
No
Not enrolled
Yes
Personal representative approached for consent
Declines
Enrolled into study
Declines
When participant regains capacity they are approached for consent
Not enrolled
Declines
Enrolled into study
Enrolled into study
Not enrolled/Withdrawal from study
Continues with follow up


Screening by clinical and research team
Participant meets inclusion criteria
~0hrs
CONSENT PROCESS
England
Do they have capacity to consent?
Yes
No
Approach participant for consent
Is a personal representative available?
No
Is a professional representative available?
No
At 30 minutes, use deferred consent
Yes
Yes
Enrolled into study
Professional representative approached for consent
First available representative approached for consent ASAP
Personal representative approached for consent
Declines
Declines
Declines
Professional representative available first
Not enrolled
Enrolled into study
Enrolled into study
Once personal representative available
When participant regains capacity they are approached for consent
Declines
Enrolled into study
Enrolled into study
Not enrolled/Withdrawal from study
Continues with follow up

5.3 WITNESSED METHODS OF OBTAINING SIGNATURES

Consent will normally be recorded in writing, dated and signed or otherwise marked by the participant or their legal representative. In most instances this will take the form of a face-to-face consent process with a wet ink signature.

If face-to-face consent is not possible or feasible, verbal consent over the phone or video-call will be utilised, this will be witnessed and recorded in writing. If a verbal witnessed consent procedure is utilised we will also attempt to obtain a written signature from the participant or their legal representative by posting the consent form to them for signature and return as described previously.

5.4 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator, or their Personal/Professional Representative (where appropriate). If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. They will have the option of withdrawal from:

i) Further blood sampling but consent to continuation of data collection from routine medical records and use of sub-study data collected up to that point

ii) All aspects of the trial but continued use of sub-study data collected up to that point.

To safeguard rights, the minimum personal information possible will be collected.

If a participant withdraws from the main study (ABC Sepsis) they will be asked whether or not they wish to be withdrawn from the sub-study.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

During this trial the following assessments will be completed:

Assessment	Screening	Baseline	12 (±4) hours*	24 (±6) hours*	30 days	90 days
Consent	X					
Eligibility	X					
Demographics, Medical History		X				
Blood samples (EDTA and PAXgene tubes)		X	X	X		
Vital signs		X	X	X		
Mortality#					X	X
Length of stay, Ward/HDU/ICU stay#					X	X
Adverse events#		X	X	X		

*after enrolment. #This data will be collected on the ABC sepsis CRF and shared with the MIS-ABC trial

6.2 BLOOD SAMPLING

Participants in the MIS-ABC trial will have samples taken at three points:

- Baseline (0 hrs): this sample will be taken at the point of enrolment into the sub-study, with the aim of characterising the inflammatory response to sepsis before, or at, the point of administration of the trial intervention.
- Second sample (12 ±4 hrs) after enrolment
- Last sample (24 ± 6 hrs) after enrolment

In each case, two samples will be taken sequentially, from the same point of access. In order to minimise burden to the participants, the study team will work with the clinical team to identify opportunities to take blood simultaneously with routine sampling, as well as identifying sampling options which use existing points of access. Examples of this include:

- Taking research samples at the same time that venepuncture is being performed for routine clinical samples (e.g. taking the research samples with the routine samples from the same 'butterfly needle')
- Taking research samples at the same time that a new, or re-sited, point of vascular access is inserted (e.g. taking the research samples when a new peripheral cannula is inserted)
- Taking research samples from an existing port of vascular access which allows sampling (e.g. taking research samples from an arterial line, a central line or a PICC).

6.3 LONG TERM FOLLOW UP ASSESSMENTS

There is no long term follow up for this study. Participants will be followed up for the ABC sepsis study using routine clinical data at 30 days and 90 days from the medical notes and this data will be shared for the analysis of the MIS-ABC study.

6.4 STORAGE AND ANALYSIS OF SAMPLES

At each sampling point during this study, two blood samples will be taken. The first is a 4mL EDTA tube, and the second is a 2.5mL PAXgene tube. From the EDTA tube of blood, we will aliquot one millilitre into cytodelics cell preservation medium for cellular phenotyping (referred to as "cells") and the remaining blood in EDTA tube will be spun down to isolate), which will be stored in aliquots for measuring cytokines.

They will be labelled using pseudonymous study identifiers and stored locally at -80ºC until recruitment ends, at which point samples will be shipped to the central laboratory (at the Royal Infirmary of Edinburgh) for analysis.

Consent will be sought for long term storage at the University of Edinburgh for all samples (i.e. PAXgene, cells and plasma), anticipated to be a period of up to 5 years. In the case of the PAXgene tube, funding is not yet secured for the planned sequencing analysis and the samples will be stored until this is possible. Because these tests include genetic analysis, explicit consent will be sought from patients with this in mind. However, the nature of the analysis will be limited to the specific patient presentation and immune response during the time studied.

7 DATA COLLECTION

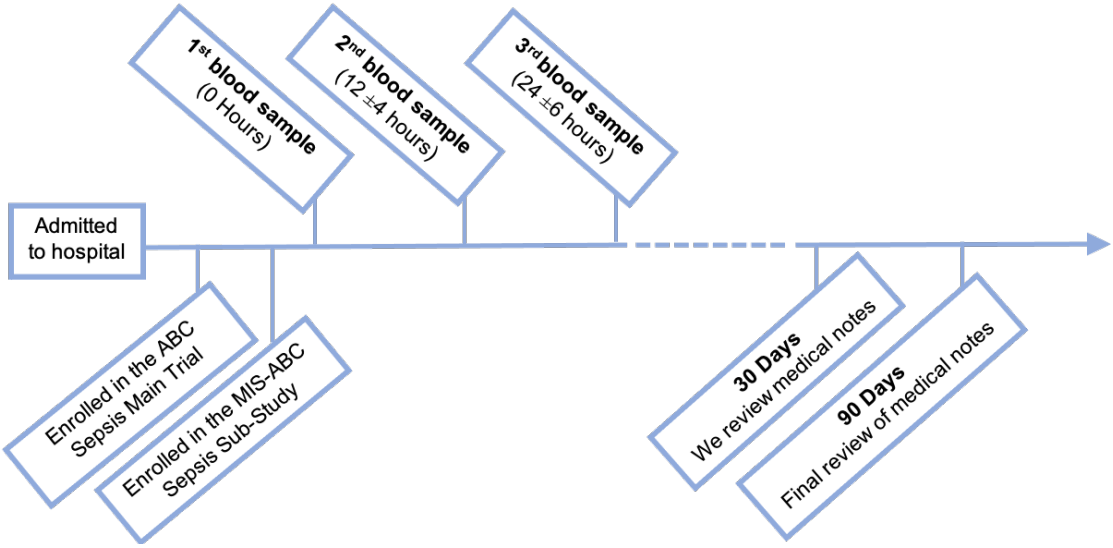
Data specific to the sub-study will be collected from consent until 90 days at a number of key points by a member of the research team:

- At informed consent, enrolment and baseline investigations

- Eligibility and consent
- 0hr blood sampling
- 0hr vital signs
- Results of nearest serum lactate measurement (if taken as part of routine care)

- At 12 (±4) hours sampling
  - 12 hour blood sampling
  - Vital signs and (±30 minutes from time of sampling)
  - Results of nearest serum lactate measurement (if taken as part of routine care)
- At 24 (±6) hours sampling
  - 24 hour blood sampling
  - Vital signs (at ±30 minutes from time of sampling)
  - Results of nearest serum lactate measurement (if taken as part of routine care)

All relevant intervention, outcome and follow up data will be collected as part of the ABC-Sepsis trial and a data sharing agreement will allow us to make use of this data.



7.1 SOURCE DATA DOCUMENTATION

Data will be collected from consent until final follow up visit.

Source data will either be study specific or routine clinical data. Study specific source data, including consent forms, eligibility criteria forms, and sampling details (e.g. timing of samples) will be recorded on the relevant pseudonymised source study data worksheets distributed to participating sites.

Clinical data, including physiological observations and blood samples taken as part of routine care, will be recorded according to local practice and transcribed onto the study data worksheets as agreed by site-specific source document plans.

7.2 CASE REPORT FORMS

Paper CRFs (study data worksheets) will be completed as the participant progresses through the study and then entered into a database on a trial database on a secure NHS computer. Scanned images of the worksheets may also be sent to the trial management team for quality assurance purposes.

Processing of samples will be recorded on 'processing logs', paper sheets which will record the time and date of processing, number of samples and person processing them. They will be shared with the trial management team in a similar manner to the study data worksheets.

Clinical outcome data will be collected as part of the ABC Sepsis study from NHS records and will include comorbidities; vital signs, routine blood results including baseline kidney function, liver function and albumin; relevant investigations or interventions including surgery, vasopressor use, renal replacement therapy, invasive ventilation, chest x-rays, prescriptions; time of start of ABC Sepsis IMP; length of stay including critical care, repeat hospitalisations, adverse events and decisions regarding treatment escalation planning and resuscitation. Detail will also be collected on the trial intervention including timing and volume of fluids. Length of stay and repeat hospitalisation will be recorded as part of follow up. These data will be shared with this sub-study in line with the ABC Sepsis data management plan for sharing and reuse.

7.3 TRIAL DATABASE

At regular intervals throughout the study, the site research teams will transcribe the paper worksheets into the trial database specifically developed for this purpose. This central database will be managed by the trial management team and kept on secure servers at the host insitution. Scanned copies of the relevant paper worksheets (i.e. containing pseudonymised study data) may be requested from site teams for quality assurance.

Following data analysis, the database will be archived by the trial management team. This archived database will be stored indefinitely on secure host institution servers once user access has been disabled. Access to the archived database will be controlled by the Chief Investigator.

8 DATA MANAGEMENT

This trial will be coordinated from the Royal Infirmary of Edinburgh. Data will be collected at each site by local investigators and uploaded to the database. If a participant or their representative withdraws a previously given informed consent or refuses to consent for continuation in the trial, or if the participant dies and no participant consent is available, the patient's data will be handled as follows: Data collected up to the point of withdrawal will be used in an intention to treat analysis.

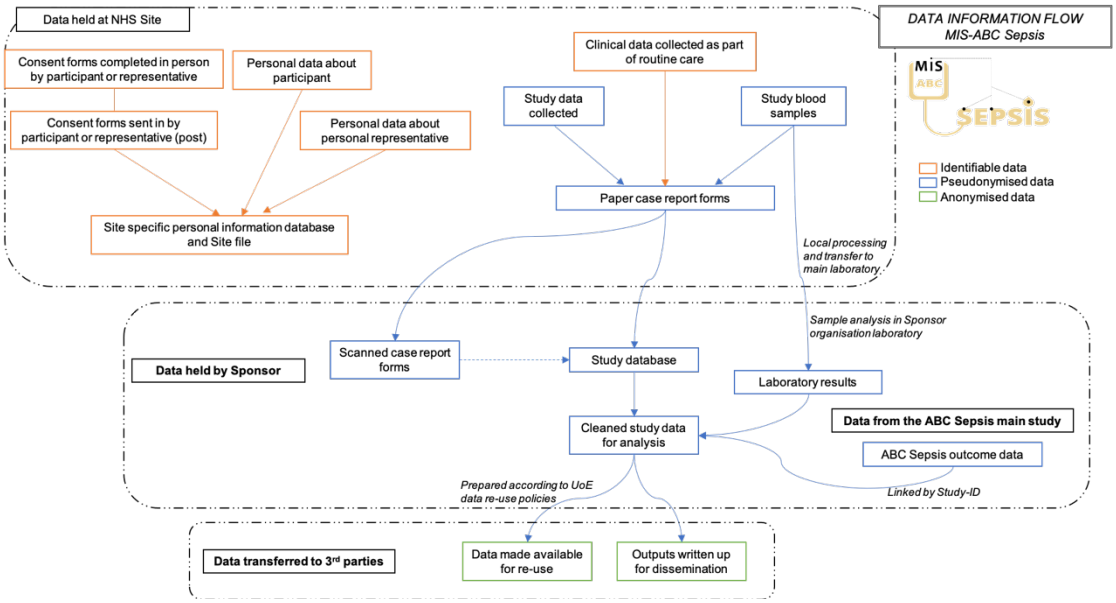
8.1 PERSONAL DATA

Local sites will also maintain a secure document as reference linking a participant's study ID with the personal information (including name, date of birth, hospital number, address, telephone number, sex at birth, GP information) of the participant. Where relevant, personal data of the personal representative will also be collected to obtain consent (including name, home address, telephone number).

The name, address and GP details will only be collected for the purposes of sending a letter to the GP informing them their participant is taking part, to send consent forms (if required), and to disseminate result of the trial (if the patient opts for this). This personal data will be kept at the study site.

Personal data will be stored by the study team on NHS computers (desktop and/or laptop). Computers will be password protected and kept in locked offices. All paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Access to the study documents will be by the study team only. Data will be entered by those staff delegated to do so on the delegation log held at site. Personal data will be stored for 5 years.

8.2 DATA INFORMATION FLOW



8.3 TRANSFER OF DATA

Personal data will not be transferred to any external individuals or organisations outside of the Sponsoring organisation.

Every effort will be made to make data available for legitimate re-use via existing University of Edinburgh systems, according to the FAIR principles [24]. Data stored on such repositories will only be those with which we can guarantee sufficient protection to participant confidentiality, as per University policies and governance systems.

8.4 DATA CONTROLLER

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

8.5 DATA BREACHES

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

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Whilst a sample size of 300 has been calculated for the main ABC Sepsis study, as this sub-study is an exploratory analysis no sample size calculation has been conducted. The majority of existing work on cytokine and RNA response focuses on sampling dates in a different context: over the course of days to weeks in patients presenting to hospital with sepsis. Our work will provide a foundation upon which to build further larger studies. We aim to recruit a minimum of 70, which has been selected because it confers a greater than 90% likelihood of incorporating 30 or more participants in the smaller group, assuming equal likelihood of

randomisation to each arm. 30 is a consensus figure arrived at by expert co-authors of the study with experience in related work in critical care research [25]. We anticipate enrolment would not continue beyond 80 participants: at this sample size there is a 99% likelihood of including at least 30 participants in each arm.

9.2 PROPOSED ANALYSES

This project is primarily an exploratory analysis. We will report results by group as defined by the treatment arm into which they are enrolled, as well as by key outcomes (e.g. mortality at 30 days, admission to ICU). No interim analyses will be conducted.

Analysis will be conducted, across treatment arms, of individual biomarkers as part of our cytokine panel, whether at individual timepoints or in terms of the change, and rate of change, from baseline results. It will also incorporate analysis of grouped variables (e.g. 'pro-inflammatory cytokines' versus 'anti-inflammatory cytokines', or those known to be representative of specific pathophysiological damage like endothelial damage), again at individual timepoints or in terms of the change, and rate of change, from baseline. Further grouping may be taken, depending on the spread of our physiological data, to determine differences between 'responders' to fluid challenge versus 'non-responders' in either treatment arm.

Taken as a whole, we will assess the accuracy of these biomarkers as predictors of our key clinical endpoints, with consideration of sensitivity, specificity and positive or negative predictive values. Receiver operator characteristic analysis will be explored for biomarkers with significant biological plausibility or which show promise in the preceding analysis. Transcriptomic data from RNA-seq will be interrogated to determine changes in RNA abundance at the gene level between sample points and by treatment arm, as well as at the transcript isoform level.

Using the inclusion criteria mentioned before, it is plausible that we will include patients who ultimately are diagnosed with a pathology other than sepsis as a reason for their presentation to hospital. The inclusion of the results of such patients in the described analyses will be decided on discussion with the broader study team in the context of the frequency of this occurrence as well as the potential bias this might incur with the specific analysis.

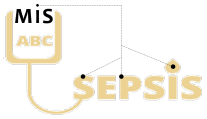
10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

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

10.2 STUDY MONITORING AND AUDIT

There is no routine monitoring or audit planned for this study.



11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 KEY ETHICAL CONSIDERATIONS

We recognise that the emergency presentation of sepsis is a challenging situation in which to conduct clinical research and it is critical that studies in such a setting are planned with ethical considerations centrally in mind. We have consulted with local patient and public involvement to both ensure acceptability of this study and optimise study documents.

11.2.1 Consent process

Emergency presentations for conditions such as sepsis are scary, uncertain and unsettling times for patients. It is fundamental to the design and conduct of this study that patient safety and dignity are the primary concerns of clinical and research teams involved in the care of these patients.

In the acute setting, where trial interventions are necessarily time dependent, participants and researchers do not have the same luxury as many outpatient or non-emergency studies. Information must be communicated, explained and considered in a shorter than usual timeframe to allow informed consent within the window where interventions relevant to this study may have greatest impact. It is a priority, and area of significant experience, of the emergency medicine research team to communicate all information participants require to make informed decisions about participation of care. The majority of the research teams involved in this work will have first-hand experience of working within emergency departments and acute admission units, as well as broad experience of recruiting and communicating in busy and challenging environments.

Beyond clear explanation of the study processes and understandable communication of risk and any deviation from standard practice, specific approaches which will be employed include: tailoring of information as guided by the patient in front of the researcher, and emphasizing the ability to opt out, ask further questions later, and to retain documents for review in the future.

A significant proportion of patients presenting with sepsis are so unwell that their capacity is temporarily impaired. Furthermore, a number of comorbidities increase the likelihood of impaired capacity due to acute illness: using consent procedures designed for the non-acute setting would see this population underserved by research conducted with such measures. ABC Sepsis is a pragmatic trial, inclusive of many degrees of comorbidity which are typically excluded from sepsis research. MIS-ABC Sepsis is similarly pragmatic, with the aim that the findings are as broadly generalizable as possible.

We see the Personal/Professional Representative mechanism as key to increasing inclusion into this area of research. However, we understand and expect that participants, and their Personal/Professional Representatives, may at times disagree or change their mind, and the withdrawal procedures have been carefully drafted to make that a clear and definitive process.

11.2.2 Burden on patients

In any research study, participants incur a somewhat increased burden. Often this is of questioning, decision making and testing. In creating the protocol for this sub-study there has been a careful balance struck between obtaining scientifically important data and following, as close as possible, routine paths of care to limit the burden we place upon participants.

In routine clinical practice when caring for patients unwell with sepsis, blood tests, physiological observations and clinical questioning and examinations are done frequently. This is particularly true for those patients who have physiological disturbances (i.e. high NEWS scores) and who require intravenous fluid therapy. Specific measures as part of this protocol like the leeway afforded to sampling times and the ability to take research and routine samples on the same blood draw mean that patients incurring additional venepuncture solely for the sake of blood samples will be a last resort. The second important area of burden, which is the discussion and information processing around informed consent at the beginning of this study process, has been designed to follow logically and concisely from the information given as part of the ABC Sepsis main study.

11.2.3 Genetic analysis

Often participants across studies are concerned about privacy implications of genetic analysis performed in research trials. Popularly, concerns around unearthing diagnoses or increased risks of disease which participants would not want to know about are cited as key concerns. Genetic material in blood samples taken as part of this sub-study will be analysed in a manner which is specific to sepsis, and in all likelihood specific to that presentation and subsequent response to treatment for sepsis.

Separately, because this genetic analysis would be conducted for the purposes of scientific research it does not need to be disclosed to an insurance company [26].

11.2.4 Relationship with the main ABC Sepsis trial

This sub-study is designed to be conducted with and alongside the ABC Sepsis trial, which has already been reviewed by a REC (Number 20/SS/0110). The investigator and management team conducting this sub-study are all involved in the main trial, with the full support of the main trial. In sites where both the main study and sub-study will take place, there is expected to be almost complete overlap in terms of the site teams undertaking the research. Collaboration and sharing of resources on all levels is envisaged to avoid waste and to ensure a streamlined process for both the studies and the participants.

An inherent risk with any feasibility clinical trial like ABC Sepsis is that the objectives are not met and funding is not secured for a sufficient trial to answer the research question. Careful planning and preparation have been done on the part of both study and sub-study to avoid this, however in the event that the main study objectives are not met, it is hoped that this sub-study will improve our mechanistic understanding of the proposed interventions. Even in the event that results from the sub-study do not provide clear mechanistic data for the interventions, they will provide important information about inflammatory processes in a population which is, as yet, incompletely understood.

11.3 INVESTIGATOR RESPONSIBILITIES

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

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

11.3.1 Informed Consent

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

Participants will receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the

participant will be performed by the Investigator or qualified delegated person, and will cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant will be given every opportunity to clarify any points they do not understand and the opportunity to ask for more information. It will be emphasised during this process that the participant may withdraw their consent to participate at any time without impacting their clinical care or loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s). The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the ISF and participant's medical notes.

In the event of consent via Personal Representative, relevant equivalent oral and/or written information will be provided to relevant individuals in that process. In this circumstance, once the participant has regained capacity, relevant oral and written information will be provided to them.

11.3.2 Study Site Staff

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

11.3.3 Data Recording

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

11.3.4 Investigator Documentation

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

11.3.5 GCP Training

All researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement as this is not a CTIMP study. GCP training status for all investigators will be indicated in their respective curricula vitae.

11.3.6 Confidentiality

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

11.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place. Data stored on a repository for re-use will be handled as described in Section 8.3 Transfer of Data.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

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

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

12.2 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

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

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

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

12.3 SERIOUS BREACH REQUIREMENTS

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

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

(b) the scientific value of the trial.

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

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's last 90 day follow up.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

No treatment is being conducted in this sub-study.

12.7 INSURANCE AND INDEMNITY

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

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

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

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. Once the study is completed, analysis performed and study shut down complete, a clinical study report will be prepared and submitted to the sponsor within 1 year of the end of the study. A published journal article may take the place of this clinical study report if agreed with the sponsor.

13.2 PUBLICATION

Investigators have the right to publish, orally or in writing, the results of the study under direction of the Chief Investigator. The results of the study, together with other mandated information, will be uploaded to the relevant clinical trial registration page (ClinicalTrials.gov) within 1 year of the end of the study.

13.3 DISSEMINATION OF RESULTS

Where participants have requested to be updated about results of the study and have consented for such contact, a summary of the results will be provided after the end of the study. Summaries of results may also be made available to Investigators and participating sites through short reports or via social media.

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