PROTOCOL

BiomArker-guided Duration of Antibiotic treatment in hospitalised PaTients with suspected **Sepsis**: the **ADAPT-Sepsis** Trial.

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NHS
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TABLE OF CONTENT **PAGE**

LIST OF TABLES **PAGE**

LIST OF FIGURES **PAGE**

TRIAL SUMMARY

Biomarker-guided duration of antibiotic treatment in hospitalised patients with suspected sepsis.

ADAPT-Sepsis Trial

Aim: To deliver a UK-wide multi-centre randomised controlled trial to determine whether treatment protocols based on monitoring daily CRP (C-reactive protein) or PCT (procalcitonin) safely allow a reduction in duration of antibiotic therapy in hospitalised adult patients with suspected sepsis.

Design: Multicentre three-arm randomised controlled trial with internal pilot.

Setting: UK acute NHS hospitals.

Target population: Hospitalised adults who have been commenced on intravenous antibiotics for sepsis.

Inclusion criteria: (a) At least 18 years old; (b) receiving intravenous antibiotics for sepsis; (c) no more than 24 hours of systemic antibiotic treatment for present sepsis episode; (d) likely to require intravenous antibiotics for at least 72 hours and (e) requirement for critical care.

Main exclusions: (a) prolonged antimicrobial therapy mandated; (b) severely immunocompromised; (c) All treatment for suspected sepsis likely to be stopped within 24 hours of its initiation because of futility (d) any patient given, or anticipated to receive an IL-6 receptor inhibitor drug (e.g. tocilizumab or sarilumab) during their acute hospital admission**.**

Health Technology: 3 protocols for guiding antibiotic discontinuation will be compared: (a) standard care; (b) standard care + daily CRP monitoring; (c) standard care + daily PCT monitoring. Standard care will be based on routine sepsis management with associated NHS antibiotic stewardship guidance. We have developed biomarker protocols, based on daily assays, adopting the best evidence from the international guidance for CRP and including NICE guidance for PCT to guide antibiotic discontinuation.

Measurement of costs and outcomes: Outcomes will be assessed to 28 days. The primary outcomes are total duration of antibiotics and safety outcome of all-cause mortality. Secondary outcomes include: escalation of care/re-admission; infection re-lapse/recurrence; dose of antibiotics; length and level of critical care stay and length of hospital stay. 90-day all-cause mortality rates will also be collected. An assessment of in-trial cost effectiveness will be performed.

Sample size: A total sample size of 2760 would be able to detect both a mean of 1-day reduction in antibiotic duration (using a mean antibiotic duration of 7 days, a pooled standard deviation of 6 days, 90% power, a significance level of 5%, with a 5% withdrawals rate) and a non-inferiority safety margin of 5.4 % (using a 1-sided significance level of 2.5%, 90% power and 5% withdrawal rate) assuming 28-day mortality is 15%.

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trials Unit
DMC	Independent Data Monitoring Committee
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit and Research Centre
ICSPRC	Intensive Care Society's Patients and Relative Committee
ICUSteps	ICU Support Teams for Ex-Patients
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PCT	Procalcitonin
PHE	Public Health England
PI	Principal Investigator
PIS	Patient Information Sheet

PPI	Patient & Public Involvement
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
ScHARR	School of Health and Related Research (University of Sheffield)
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TNO	(Participant) Trial Number
TSC	Independent Trial Steering Committee
WCC	White Cell Count
WCTU	Warwick Clinical Trials Unit

1 BACKGROUND

1.1 Trial background

1.1.1 Sepsis

Sepsis results from overwhelming reactions to microbial infections where the immune system initiates dysregulated responses that can lead to remote organ dysfunction, shock and ultimately death (1). The international incidence of sepsis is estimated at 300 per 100,000 per year (2), suggesting that there are around 200,000 cases a year in the UK. Sepsis is important to both patients and the NHS, because it is a major cause of avoidable deaths, long term physical and psychological morbidity and cost (3). Survival from sepsis, for example, is about 75% if recognised and treated promptly (4). Mortality increases if initiating treatment is delayed (5). The Parliamentary and Health Services Ombudsman highlights the importance of early recognition and treatment for sepsis survival (3), which has led directly to the initiation of a number of NICE guidance projects, a NCEPOD report (2) and a new NHS standards-of-care framework (6), all of which will form the background to and rationale for our proposed trial.

1.1.2 Current standard of care: emergency antibiotic initiation

Early, appropriate antimicrobial treatment for infection is a crucial part of emergency interventions aimed at surviving sepsis (7). Choosing the right antimicrobial drugs and doses is crucial because the risk of death is associated with a two to fourfold increase when inappropriate antibiotic therapy is given (8). However, objective microbiological confirmation of infection can be challenging, with culture results taking a number of days to become available and with only 40% being positive in patients with sepsis (2). Viral and fungal causes of sepsis are thought to be important. However, a recent enquiry into sepsis in the NHS was unable to find evidence for this, with bacterial pathogens frequently encountered (2). Therefore, for patients with suspected sepsis it is recommended that empirical intravenous broad-spectrum antibiotics are commenced within 1 hour: an NHS standard incentivised by a payment framework (6).

1.1.3 Current standard of care: antibiotic duration for sepsis

Once commenced, the overall duration of antibiotic treatments is less certain. Fixed and long duration antibiotic courses (up to 10-14 days) have been widely used in the NHS because clinical signs and microbiology culture tests are not useful to monitor treatment efficacy to guide the decision to stop antibiotics (9). Daily clinical review of patient progress and treatments, performed alongside microbiology results and advice, do provide opportunities to limit patient exposure to broad-spectrum antibiotics while tailoring effective therapy for a proven infection – the so-called ‘Start smart - then focus’ approach to antibiotic use and stewardship recommended by Public Health England (PHE) (10) and NICE (9).

1.1.4 Introducing biomarker-guided antibiotic treatment in sepsis

Readily available circulating serum proteins (biomarkers) such as C-reactive protein (CRP) and procalcitonin (PCT) – the most intensively researched biomarkers - are often raised in sepsis and usually fall in response to effective antibiotic treatment (11). This provides a potential opportunity to personalise antibiotic duration which could lead to reductions in population antibiotic usage, adverse effects for patients, improved healthcare resource utilisation and downstream effects relating to antimicrobial resistance - an urgent priority. However, these biomarkers are part of the patient’s complex inflammatory response triggered not only by infection but by other stimuli such as trauma and surgery; ongoing inflammation does not necessarily reflect ongoing active infection. Thus, longer than necessary courses of antibiotics may be administered if guided solely by raised levels of these biomarkers as part of antibiotic ESCALATION protocols (12). Biomarker-guided

antibiotic DISCONTINUATION protocols in sepsis have been associated with shorter treatment durations in other healthcare systems internationally (7, 13), but studies are low quality, often restricted to pre-defined patient groups (e.g. adults with lower respiratory tract infections) and conducted solely in a single healthcare setting (e.g. intensive care) with associated lack of generalisability and with uncertain relevance to current NHS practice.

1.2 Rationale

1.2.1 Rationale for trial

Our proposed research is important and timely for the NHS and its patients because the early and potentially prolonged use of broad-spectrum antibiotics is increasing, linked to improvements in identifying and treating suspected sepsis as an emergency. However, the recommended duration of antibiotic therapy for sepsis is based on evidence of low quality that may lead to an overuse of antibiotics, contributing to the development of antimicrobial resistance, a national and global priority. Shorter courses of antibiotic therapy would be associated with lower volumes of antibiotic use with expected reductions in adverse effects for patients, reductions in healthcare resource utilisation, and wider downstream benefits for antimicrobial resistance (14). This research area is also relevant to the UK 5-year Antimicrobial Resistance Strategy (15) which aims to protect the effectiveness of currently available antibiotics for the whole UK population and develop treatment strategies that will prolong the utility of new antimicrobial pharmaceuticals as they emerge.
Our trial will focus on the use of both CRP and PCT-guided antibiotic treatment duration in sepsis from a wide range of infection origins for the widest possible NHS applicability and impact. The evidence-base for PCT-guided antibiotic duration in sepsis was considered in a recent NIHR HTA commissioned systematic review and cost-effectiveness analysis (13) with subsequent NICE guidance (16) concluding that there is currently insufficient evidence to recommend routine adoption in the NHS and that further research on PCT testing was recommended for guiding decisions to stop antibiotic treatment in people with confirmed or highly suspected sepsis. In addition, NICE recognised that CRP is very likely to be monitored in the NHS during sepsis care, but there is a near absence of prospectively tested CRP-based algorithms and interventional data regarding efficacy and safety for guiding antibiotic duration.

1.2.2 PCT and CRP-guided antibiotic discontinuation protocols in sepsis

The health technologies being assessed are laboratory measured PCT and CRP-guided antibiotic discontinuation protocols aimed at safe reductions in antibiotic treatment duration for the management of patients with sepsis.

A NIHR HTA commissioned systematic review (13) has reported a summary of algorithms from intervention studies for PCT-guided antibiotic treatment duration in sepsis. All studies were performed outside the UK and used PCT algorithms with multiple decision thresholds to guide antibiotic treatment in the intervention arm, with final treatment decisions always remaining at the discretion of the treating clinician. The details of the PCT algorithm varied between studies; however, all discontinuation algorithms included a component that encouraged or strongly encouraged discontinuation of antibiotics when the PCT level was < 0.25µg/l and/or encouraged discontinuation of antibiotics when the PCT level was < 0.5µg/l. Discontinuation studies reported measuring PCT at baseline and daily or every 2 days until discontinuation, discharge or death. A fall in PCT from baseline by ≥ 80% was incorporated into some algorithms to encourage antibiotic discontinuation. One study reporting after the systematic review used an antibiotic discontinuation threshold < 0.1µg/l in the setting of suspected severe bacterial infection or sepsis in a multi-centre Australian Intensive Care intervention trial (17). The lack of effect in this study is widely regarded as

unsurprising (16) as the applied decision threshold was much lower than those typically used for patients with sepsis (11).

To the best of our knowledge, there is only one interventional study on CRP-guided antibiotic treatment discontinuation in sepsis (18). A CRP-based algorithm was compared with a PCT-guided algorithm in determining antibiotic duration – with both algorithms including antibiotic discontinuation rules based on relative declines and absolute biomarker thresholds. The CRP protocol had an absolute treatment discontinuation threshold at $\leq$ 25mg/l and relative discontinuation threshold when CRP fell by at least 50% from baseline. We could find no other prospectively tested CRP-based algorithm reporting interventional data regarding efficacy and safety for guiding antibiotic discontinuation.

1.2.3 CRP and PCT assays and NHS use for the management of sepsis

We have surveyed NHS medical and surgical professionals who regularly manage patients with sepsis across the UK through the Intensive Care Society and the Association of Surgeons of Great Britain and Ireland. From 380 replies, only 7 respondents (2%) measured PCT in every patient with sepsis on a daily basis, 286 respondents (75%) never or rarely used PCT, with the remainder using PCT occasionally or in selected patients. We received 40 replies describing local protocols for antibiotic discontinuation based on serial PCT tests. These PCT protocols were clearly consistent with the international intervention trial literature (13).

Our survey returns also indicated that CRP is commonly measured throughout the NHS in patients with sepsis (with 197 (52%) using it daily in every patient, 149 (39%) using it occasionally or on selected patients, and 34 (9%) never or rarely). Despite frequent but variable use of CRP testing, there were no reports of established local practices or protocols for antibiotic discontinuation based on CRP. Furthermore, there was a clear desire to establish and test a suitable protocol derived from the available international literature (with the majority of respondents (70%) wishing to take part in an interventional study involving both CRP and PCT-guided protocols to guide antibiotic duration in sepsis).

We also surveyed NHS laboratory services to establish the prevalence of both serum CRP and PCT measurements and to discover the likely available laboratory analytical platforms ready for study implementation. Receiving replies from 55 NHS services across the UK, CRP assays were commonly requested from emergency departments, acute medical and surgical admission units/wards and critical care units. We also gathered important information about the common analytical platforms for CRP across the NHS. When considering PCT laboratory assay platforms, 22 services replied with only 4 (18%) offering routine analysis for PCT, predominantly from critical care units. Recent NICE guidance (16) reports PCT assay platforms to be technically comparable, using the same capture and detection antibodies in an immunoassay and they have been standardised. NICE also confirmed in their guidance that NHS laboratories should have flexibility in the choice of PCT analyser for future intervention studies. Therefore, where necessary, we will work with recruitment centre laboratories to establish a PCT assay based on the availability of a preferred local laboratory platform.

1.3 Hypothesis

Hospitalised adult patients already receiving empiric intravenous antibiotics for suspected sepsis, who are treated using an antibiotic discontinuation protocol based on either CRP or PCT, will have safe decreases in antibiotic treatment duration compared with those treated with standard care alone.

1.4 Need for a trial

Our proposed trial is important and timely for the NHS and its patients because the early and potentially prolonged use of broad-spectrum antibiotics is increasing, linked to improvements in identifying and treating suspected sepsis as an emergency. However, the recommended duration of antibiotic therapy for sepsis is based on evidence of low quality that may lead to an overuse of antibiotics, contributing to the development of antimicrobial resistance, a national and global priority. Shorter courses of antibiotic therapy would be associated with lower volumes of antibiotic use with expected reductions in adverse effects for patients, reductions in healthcare resource utilisation, and wider downstream benefits for antimicrobial resistance (14). This research area is also relevant to the UK 5-year Antimicrobial Resistance Strategy (15) which aims to protect the effectiveness of currently available antibiotics for the whole UK population and develop treatment strategies that will prolong the utility of new antimicrobial pharmaceuticals as they emerge.
The ADAPT-Sepsis trial has been designed and funded to address the brief of a recent NIHR Health Technology Assessment (HTA) commissioning call (HTA number 15/99).

1.5 Exploratory mechanistic study → RISC-Sepsis

A mechanistic study (RISC-sepsis) will be embedded within the ADAPT-sepsis trial (see section 2.13 for full details) Sepsis is characterised by dysregulated pro-inflammation and anti-inflammation. The abnormal anti-inflammatory state or 'sepsis-induced immunosuppression' is identified by abnormalities in leucocyte cell surface marker expression.

We hypothesise that patients with sepsis-induced immunosuppression will have longer duration of antibiotics, due to persistently raised PCT and CRP, and have more hospital-acquired infections and thereby further increase antibiotic use at 28-days. Sepsis-induced immunosuppression will be defined as the presence of abnormalities in two or more leucocyte cellular markers for 3 or more days.

1.6 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to the UK Policy Framework for Health & Social Care Research (2017). It will also comply with all applicable UK legislation and University of Warwick Standard Operating Procedures (SOPs). For sponsorship related processes the sponsor (University of Manchester) SOPs will be used. All data will be stored securely and held in accordance with Data Protection Act 2018.

Many patients with sepsis will be unable to give informed consent due to alterations in consciousness and cognition caused by illness and, in some cases, therapeutic sedation. Consent will therefore be obtained in line with legal requirements for obtaining consent in patients without capacity in England & Wales (Mental Capacity Act 2005), and in Scotland (Adults with Incapacity (Scotland) Act 2000). Procedures for consent are different in the two jurisdictions (England & Wales; and Scotland). Consent processes in Northern Ireland follow common law. For our proposed trial, the consent processes used in England & Wales will be used in Northern Ireland, with the exception that Personal Consultee assent will be taken and no Nominated Consultees will be appointed. These procedures will be updated in line with updated legislation.

Some patients will have capacity to consent. Under these circumstances the consent process, to occur within 24 hours of the patient receiving their first antibiotics, will include: assessment and documentation of capacity by a trained member of a research team; providing written information about the study; allowing sufficient time for the patient to understand the material and ask questions; obtaining written informed consent.

1.7 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, **357**: 1191-1194).

2 TRIAL DESIGN

2.1 Trial flow diagram

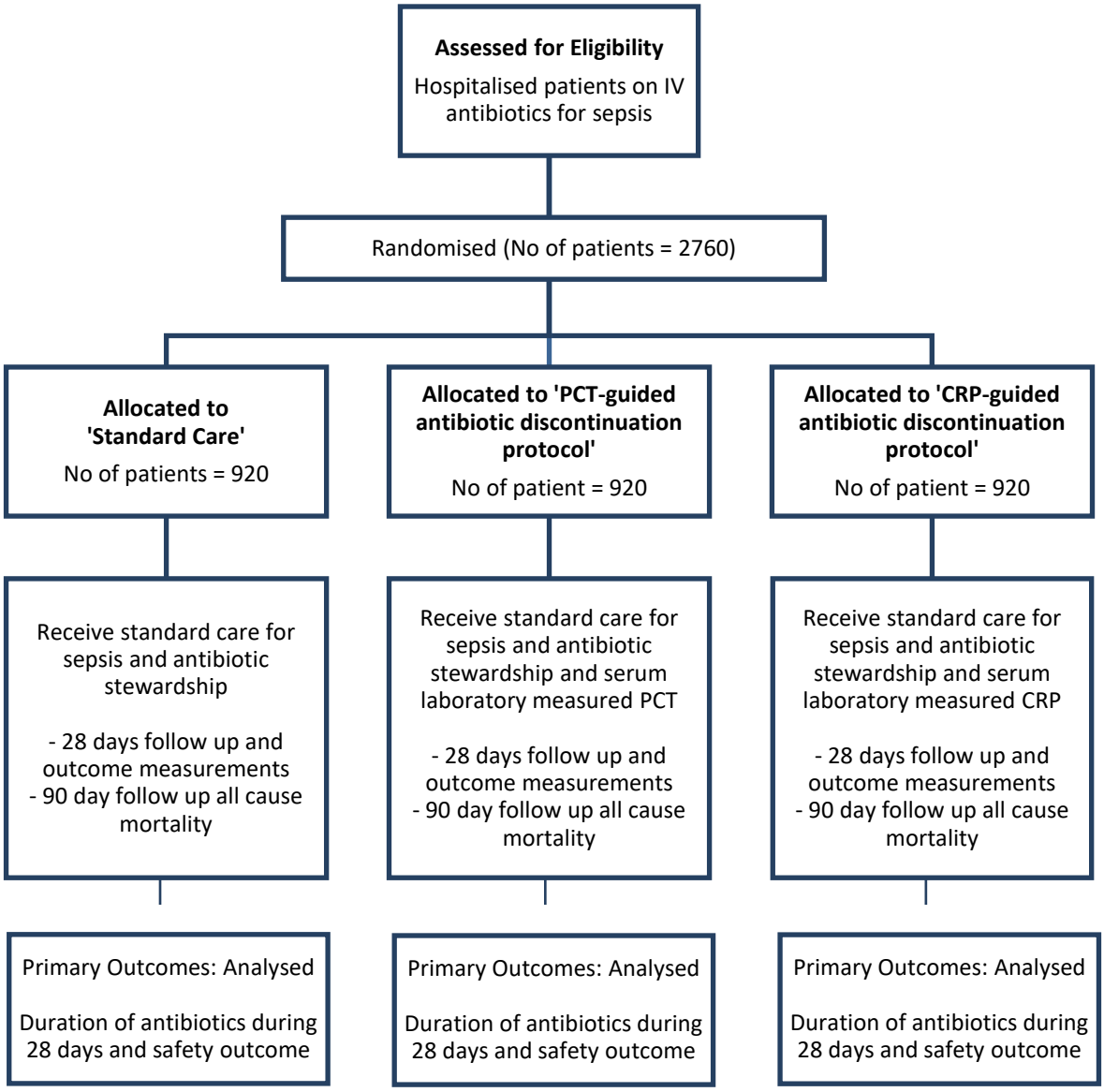

Figure 1 Trial flow diagram

2.2 Aims and objectives

We propose to deliver a UK-wide multi-centre randomised controlled trial to determine whether a treatment protocol based on monitoring CRP or PCT safely allow a reduction in duration of antibiotic therapy in hospitalised adult patients with suspected sepsis.

2.2.1 Primary objectives

The primary objective of this trial is to determine whether treatment protocols based on monitoring CRP or PCT in hospitalised adult patients with suspected sepsis reduces the duration of antibiotic therapy (superiority) while maintaining treatment safety (non-inferiority) as measured by 28-day mortality.

2.2.2 Secondary objectives

Secondary objectives of the trial are to explore whether the treatment protocols:

- reduce antibiotic exposure (defined daily dose);
- reduce critical care and hospital length of stay;
- are adhered to during routine clinical practice;
- have no effects on all-cause mortality (at 28 and 90 days post randomisation);
- have no effects on re-lapse and recurrence rates (from day 1 to 28 post randomisation);
- have no effects on unscheduled care escalation or re-admission (from day 1 to 28 post randomisation);
- reduce acquisition cost of antibiotics;
- are cost-effective in the NHS setting.

2.3 Outcome measures

2.3.1 Effectiveness and safety outcomes

Primary effectiveness and safety outcome measures:

- Total duration of antibiotic treatment to 28 days following randomisation (superiority) measured in days (24-hour time periods from randomisation) as primary clinical effectiveness outcome

- 28-day all-cause mortality (non-inferiority) following randomisation as primary safety outcome

Secondary effectiveness and safety outcome measures to 28 days following randomisation:

- Antibiotic duration and dose for sepsis episode (duration in 24-hour time periods from randomisation and dose measured as Defined Daily Dose)
- Antibiotic dose (measured as Defined Daily Dose)
- Unscheduled care escalation/re-admission
- Infection relapse/recurrence requiring further antibiotic treatment
- Super-infection defined as new infection at a different anatomical site
- Suspected antibiotic adverse reactions
- Time to ‘fit’ for hospital discharge

If the patient is discharged to another hospital or to the community within 28 days following randomisation, the local research team will contact the patient and their treating health care

professional (hospital physician or General Practitioner) to collect outstanding information about the stated primary and secondary outcomes.

All-cause mortality rates at 90 days will be collected using NHS Digital and the Intensive Care National Audit and Research Centre.

2.3.2 Health care system benefit outcomes

- Assessment of in-trial cost effectiveness (see section 6.9)
- Critical care unit length and level of stay (measured as number of Level 1, 2 and 3 days) (34)
- Hospital length of stay (days)

2.3.3 Safety reporting

- Adverse event data and reporting (see section 4)

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria (must meet all)

1. Hospitalised adult patients at least 18 years of age;
2. Up to 24 hours of initiation of empiric intravenous antibiotic treatments for a suspicion of sepsis (i.e. "**suspected sepsis**" – see trial definition below);
3. Likely to remain hospitalised and receiving intravenous antibiotic treatment for at least the next 72 hours;
4. Requirement for critical care.

Suspected sepsis definition: Within the context of this study, '**suspected sepsis**' is defined as 'acute organ dysfunction associated with suspected infection' (1). We do not mandate a definition for 'acute organ dysfunction' and patient information underpinning local clinical decisions will be captured as part of the Case Report Form (CRF) which will include the Sequential Organ Failure Assessment (SOFA) score.

2.4.2 Exclusion criteria

1. More than 24 hours since receiving first empiric intravenous antibiotic treatments for a suspicion of sepsis;
2. Prolonged (greater than 21 days) antimicrobial therapy mandated (e.g. for endocarditis, cerebral/hepatic abscess, tuberculosis, osteomyelitis);
3. Severely immunocompromised (e.g. neutropenia (not caused by sepsis), less than 500 neutrophils/microliter);
4. All treatment for suspected sepsis likely to be stopped within 24 hours of its initiation because of futility;
5. Any patient given, or anticipated to receive an IL-6 receptor inhibitor drug (e.g. tocilizumab or sarilumab) during their acute hospital admission;
6. Consent declined;
7. Previously enrolled in this trial.

2.5 Co-enrolment

Co-enrolment of ADAPT-Sepsis participants onto other intervention studies will be considered where there is no possible conflict with the ADAPT-Sepsis trial objectives. A list of appropriate and agreed studies will be produced at a national level to guide co-enrolment. Co-enrolment will be discussed and confirmed with sites at the time of site set-up and monitored throughout the recruitment phase. In addition, the CI will review the protocols for other studies at sites e.g. observational studies and will consider co-enrolment in conjunction with the Trial Management Committee where appropriate.

2.6 Participant identification / Screening

Hospitalised adult patients commenced on intravenous antibiotic treatment, within the previous 24 hours, for the management of suspected sepsis, who require critical care, will be screened against the inclusion and exclusion criteria for eligibility.

2.7 Informed consent

In many cases it will not be possible to obtain prospective consent from the patient at the time of enrolment. This is due to the fact that many patients will have a reduced level of consciousness due to their illness or due to sedative medications used as part of their treatment.

2.7.1 Patient Consent

If possible, informed consent will be obtained from the patient. The patient will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the Participant Information Sheet (PIS). Informed patients will be given an adequate amount of time to consider their participation in the trial (within the constraints of the inclusion criteria). If the patient decides to participate in the trial they will be asked to sign the Patient Consent Form, together with the responsible clinician/researcher. The patient will retain one copy of the signed Consent Form. Another copy will be placed in the patient's medical records whilst the original will be retained in the Trial Site File. Monitoring for continued consent will continue throughout the period that antibiotics are being received by the patient. Patients are expected to have been transferred and/or discharged up until the 28-day and 90-day data collection points and will be assumed (if not withdrawn before this point) to have given consent to these data collection points. Fluctuating capacity is anticipated for this patient group. Any patients who are initially able to consent for themselves will be asked to identify a person who knows them well in order to support with monitoring of their ongoing consent, alongside standard care.

Where there are concerns regarding risk of infection transmission (i.e. due to the COVID-19 pandemic), verbal consent only will be sought from the patient and documented on a study form and in the patient hospital records by the person taking consent.

<u>In England, Wales and Northern Ireland</u>

2.7.2 Personal Consultee Declaration

If the patient is unable to give consent or, in Northern Ireland, loses capacity, advice will be sought from the patient's Personal Consultee, who may be a relative, partner or close friend. This is in line with the legal requirements for obtaining consent in patients without capacity in England and Wales (Mental Capacity Act 2005). Consent processes in Northern Ireland follows common law. Where it

is found that a patient does not have the capacity the clinical and research team will work together to identify a Personal Consultee who will be contacted by telephone or met whilst visiting the patient on the ward. The Personal Consultee will be informed about the trial by the responsible clinician or a delegated member of the research team and provided with a copy of the Consultee Information Sheet and asked to give an opinion as to whether the patient would object to taking part in medical research. The Consultee will be given adequate time (within the constraints of the inclusion criteria) to consider the patient's participation in the trial. If the Consultee decides that the patient would have no objection to participating in the trial they will be asked to sign the Consultee Declaration Form together with the consenting clinician / researcher. The Consultee will retain a copy of the signed Declaration Form. A second copy will be placed in the patients' medical records whilst the original will be retained in the Trial Site File.
If the Personal Consultee has been contacted by telephone the responsible clinician or delegated member of the research team will inform them about the trial, a copy of the Information Sheet will also be sent to the Consultee via email for their consideration. In order to allow adequate time for the Consultee to consider the trial a follow-up phone call may be made and if at this time the Consultee decides that the patient would have no objection to participating in the trial they will be asked to provide a verbal declaration. The verbal declaration should be obtained in the presence of an impartial witness i.e. a person who is independent of the study and who cannot be unfairly influenced by people involved with the study. Both, the Investigator or nominee obtaining consent, and the witness will sign the declaration form. Consent will be later re-confirmed with the Representative at the next visit/contact. This process must be documented clearly in the medical notes. When the Personal Consultee attends the site they then will be asked to provide written advice by signing the Declaration form. This process must be documented clearly in the medical notes. Patients and Personal Consultees will be monitored for continued lack of objection and/or patient's ability to consent for themselves throughout the period that antibiotics are being received by the patient. Patients are expected to have been transferred and/or discharged up until the 28-day and 90-day data collection points, consent will be assumed under the signed Declaration Forms (unless withdrawn before this point) to continue to data collection points.

2.7.3 Nominated Consultee Declaration (excluding Northern Ireland)
If the patient is unable to give informed consent and attempts to meet and discuss with a Personal Consultee have failed then a nominated Consultee, who is not connected with the conduct of the Trial may act as a nominated/Professional Consultee.

The Nominated Consultee will have received information about the trial, from a member of the research team, prior to considering trial participation for an individual patient. A copy of the Consultee Information Sheet (CIS) will be provided each time an individual patient is to be considered. The patient's treating physician, with the support of the research team will determine the patient's eligibility to enter the trial and a Nominated Consultee will advise as to whether the patient would decline to take part if he/she had capacity. The patient's lead treating physician may act as a Nominated Consultee only if they have no connection with the conduct of the trial and therefore would have a dual role in both determining eligibility and considering the patient's participation. The Nominated Consultee, together with the researcher will sign and retain one copy of the signed Consultee Declaration Form, the original will be retained in the Trial Site File. If a relative, partner or close friend should subsequently visit the patient, after enrolment and before the patient has regained capacity, they should be informed about the patient's participation and invited to take over the role of Consultee and be informed about the retrospective consent process. Patients will be monitored and Nominated Consultees will be updated for continued lack of objection and/or patient's ability to consent for themselves throughout the period that antibiotics

are being received by the patient. Patients are expected to have been transferred and/or discharged up until the 28-day and 90-day data collection points, consent will be assumed under the signed Declaration/Assent form (unless withdrawn before this point) to continue to data collection points.

2.7.4 Retrospective Patient Information / Consent

Patients, for whom an opinion is given by a Consultee, will be monitored in line with GCP and if they gain capacity by the time of primary hospital discharge, or by 28 days from randomisation, (whichever is earliest) they will be informed of their participation in the trial by the responsible clinician or a member of the research team. The clinician / researcher will discuss the study with the patient and the patient will be given a copy of the Retrospective PIS to keep. The patient will be asked for consent to continue follow-up in the trial or will be supported if they wish to withdraw, it will be confirmed that data already collected will be retained by default unless the Participant or their Consultee requests otherwise. If consent is given, the patient will be asked to sign the retrospective Consent Form. The patient will retain one copy of the signed Consent Form. Another copy will be placed in the patient's medical records whilst the original will be retained in the Trial Site File. If the patient does not want to continue follow-up in the study no further clinical data beyond that time-point or new samples will be collected.

<u>In Scotland</u>

2.7.5 Guardian/Welfare Attorney Consent

Patients who meet the eligibility criteria for this study are not expected to have the ability to consent for themselves. The study is of low risk and is expected to make a significant scientific contribution. Where it is found that a patient does not have capacity, the clinical and research team will work together to identify an appointed Guardian or Welfare Attorney who will be contacted by telephone or met whilst visiting the patient on the ward in line with the Adults with Incapacity (Scotland) Act 2000. A copy of the PIS will be provided, adequate time (within the constraints of the inclusion criteria) to consider the patient's participation in the trial will be given. If the Guardian/Welfare Attorney decides that the patient can participate in the trial and there is no indication from the patient of unwillingness or objection to participate, the Guardian/Welfare Attorney will be asked to sign the Guardian/Welfare Attorney Consent Form together with the consenting clinician/researcher. The Guardian/Welfare Attorney will retain a copy of the signed Consent Form. A second copy will be placed in the patients' medical records whilst the original will be retained in the Trial Site File. If the appointed Guardian or Welfare Attorney has been contacted by telephone the responsible clinician or delegated member of the research team will inform them about the trial, a copy of the Information Sheet will also be sent to the Representative via email for their consideration. In order to allow adequate time for the Representative to consider the trial a follow-up phone call may be made and if at this time the Representative decides that the patient would have no objection to participating in the trial they will be asked to provide a verbal consent. When the Representative attends the site they then will be asked to provide written advice/consent by signing the Consent form. Verbal consent should be obtained in the presence of an impartial witness i.e. a person who is independent of the study and who cannot be unfairly influenced by people involved with the study. Both, the Investigator or nominee obtaining consent, and the witness will sign the consent form. Consent will be later re-confirmed with the Representative at the next visit/contact. This process must be documented clearly in the medical notes. Monitoring for continued consent will take place throughout the period that antibiotics are being received by the

patient. Patients are expected to have been transferred and/or discharged up until the 28-day and 90-day data collection points and will be assumed (if not withdrawn before this point) to have given consent to these data collection points.

2.7.6 Nearest Relative Consent

If a Guardian or Welfare Attorney has not been appointed for the patient, then their nearest relative maybe approached. The nearest relative will be informed about the trial by the responsible clinician or a member of the research team and provided with a copy of the Nearest Relative Consent CIS. The Patient's relative will be given adequate time (within the constraints of the inclusion criteria) to consider the patient's participation in the study. If the relative decides that the patient could participate, and there is no indication from the patient of unwillingness or objection to participate, the relative will be asked to sign the Nearest Relative's Consent Form together with signature by the consenting clinician/researcher. The Relative will retain a copy of the signed Consent Form. A second copy will be placed in the patients' medical records whilst the original will be retained in the Trial Site File. If the Nearest Relative has been contacted by telephone the responsible clinician or delegated member of the research team will inform them about the trial, a copy of the Information Sheet will also be sent to them via email for their consideration. In order to allow adequate time for them to consider the trial a follow-up phone call may be made and if at this time they decides that the patient would have no objection to participating in the trial they will be asked to provide a verbal consent. When/if the nearest relative attends the site they then will be asked to provide written consent by signing the Consent form. Verbal consent should be obtained in the presence of an impartial witness i.e. a person who is independent of the study and who cannot be unfairly influenced by people involved with the study. Both, the Investigator or nominee obtaining consent, and the witness will sign the consent form. Consent will be later re-confirmed with the Nearest Relative at the next visit/contact. This process must be documented clearly in the medical notes. Monitoring for continued consent will take place throughout the period that antibiotics are being received by the patient. Patients are expected to have been transferred and/or discharged up until the 28-day and 90-day data collection points and will be assumed (if not withdrawn before this point) to have given consent to these data collection points.

2.7.7 Recovered Capacity

Patients, for whom an opinion is given by a close relative (in a small number by a Guardian /Welfare Attorney), will be monitored in line with GCP and if they gain capacity by the time of primary hospital discharge, or by 28 days from randomisation, (whichever is earliest) they will be informed of their participation in the trial by the responsible clinician or a member of the research team. The clinician / researcher will discuss the study with the patient and the patient will be given a copy of the Recovered Capacity PIS to keep. The patient will be asked for consent to continue follow-up in the trial or will be supported if they wish to withdraw, it will be confirmed that data already collected will be retained by default unless the participant or their Guardian/Welfare Attorney or Relative requests otherwise. If consent is given, the patient will be asked to sign the Recovered Capacity Consent Form. The patient will retain one copy of the signed Consent Form. Another copy will be placed in the patient's medical records whilst the original will be retained in the Trial Site File. If the patient does not want to continue follow-up in the study no further clinical data beyond that time-point or new samples will be collected.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

2.8 Randomisation

2.8.1 Randomisation method

Randomisation will be provided by the Programming Team at the Warwick Clinical Trials Unit. A computer-generated randomisation sequence will be generated by the minimisation method. Patients will be randomised in a ratio of 1:1:1 to PCT: CRP: Usual care. The randomisation allocation will be made following consent processes and baseline assessments. Stratification factors will be (i) sepsis severity (sepsis or septic shock (1)), (ii) recruitment centre and (iii) surgery within the last 72 hours or not.

Randomisation will be available via a 24-hour web-based system.

2.8.2 Post-randomisation withdrawals and exclusions

Participants may be discontinued from the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they will be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Patients may be withdrawn from the trial due to the following criteria:-

- Patient and/or Consultee/Guardian/Welfare Attorney withdrawal
- Lead Clinician opinion
- Following Trial Steering and/or Data Monitoring Committee recommendation for withdrawal of one or more arms of the Trial
- Warwick CTU monitor recommendations based on site compliance to the Protocol
- Patient found to be ineligible post randomisation e.g. patient found to have received more than 24 hours of antibiotics following randomisation, patient identified as requiring long term antibiotics (>21 days), patient received IL-6 blocking drugs prior to randomisation and/or during the intervention period (when biomarkers are being measured).

2.9 Trial interventions

2.9.1 Trial group interventions

Patients will be randomised to one of two intervention groups (CRP or PCT guided antibiotic duration) or a standard care (control) group.

Intervention

Following consent procedures, patient blood collection (minimum of 2 ml research sample per day) and serum laboratory testing of either CRP, PCT or 'no laboratory test' (control group) will commence within the first 24 hours following the initiation of intravenous antibiotics for suspected sepsis (the baseline measurements). Daily blood sampling, laboratory testing and subsequent advice in every patient will continue until antibiotics have been discontinued, and will not recommence if antibiotics are subsequently re-introduced within the 28-day study period following patient randomisation. If a participant is discharged from hospital on a course of antibiotics for the initial sepsis episode, the trial intervention will cease at the time of discharge, they will continue to be followed up by the site until 28 days post randomisation and then via data linkage for all-cause mortality at 90 days post randomisation. Samples will be collected from patients randomised to the control group in order to maintain blinding procedures. Phlebotomy and samples will be handled in line with agreed local standard care practice.

The clinicians responsible for managing patients will receive daily standardised written advice on either continuing standard care or on antibiotic discontinuation from the local research team. Advice will be based on daily serum testing of either (a) procalcitonin or (b) C-reactive protein or (c) 'no test' (control group). The antibiotic discontinuation protocols are as follows, described alongside identical standardised advice for each group:

PCT protocol	CRP protocol	Advice for PCT and CRP protocols	Advice for control group
Standard care + daily serum PCT measurement until antibiotic discontinuation	Standard care + daily serum CRP measurement until antibiotic discontinuation	Written advice delivered daily by local research team to treating clinician until antibiotic discontinuation	Written advice delivered daily by local research team to treating clinician until antibiotic discontinuation
PCT < 0.25µg/l	CRP < 25mg/l	*"Protocol **STRONGLY SUPPORTS** stopping antibiotics"*	*"Protocol supports usual care"*
PCT fall by ≥80% from baseline or PCT ≥ 0.25 & ≤ 0.50 µg/l	CRP fall by 50% from baseline	*"Protocol **SUPPORTS** stopping antibiotics"*	*"Protocol supports usual care"*
PCT does not meet above criteria	CRP does not meet above criteria	*"Protocol supports usual care"*	*"Protocol supports usual care"*

Table 1: Trial antibiotic duration protocols

Standard care

Patients recruited to both control and intervention arms will receive standard NHS care for sepsis and antibiotic stewardship based on Public Health England (PHE) guidance (10). Standard sepsis care (7) will involve immediate fluid treatment to correct hypovolaemia, vasoactive drugs to help correct hypotension, timely treatment of sepsis source (e.g. drainage of infected fluid collections); and organ support according to need. Patients will be reviewed daily by their medical team with documented decisions on antibiotic treatment guided by standard clinical assessment and review of microbiological culture results. Routinely available laboratory data, such as white blood cell counts, will remain part of standard care for all patients recruited to our proposed trial because these are part of the current standard of NHS care for patients with sepsis (10). Through the trial Case Report Form, local investigators will record any clinical use of routine data informing antibiotic duration decisions and trial protocol adherence will be assessed and reported. Multi-disciplinary antibiotic stewardship review is expected to occur at least every 72 hours for patients receiving intravenous antibiotics, as recommended by PHE guidelines (10). Daily clinical review of all patients with sepsis, as a standard-of-care, will allow incorporation of the intervention protocols for daily assessment of antibiotic discontinuation described in Table 1.

2.9.2 Compliance/contamination

(a) screening; (b) recruitment; (c) reasons for exclusion and (d) protocol adherence will be audited throughout the study by using data recorded in screening logs, Case Report Forms (CRFs) and during site visits. Protocol adherence will be captured using specific data recorded in the CRFs of adherence to biomarker-guided advice on antibiotic discontinuation – and reasons for non-adherence will be documented if it occurs.

A particular challenge for trials incorporating biomarker-guided antibiotic discontinuation protocols in sepsis is the variable but common use of CRP monitoring in this patient group, as identified by our recent surveys. However, it is clear that CRP monitoring is not used in the NHS as part of any defined discontinuation protocols and it is not always used on a daily basis for patient monitoring. Therefore, we expect study centres to have a position of equipoise during the trial in terms of biomarker (CRP and PCT)-guided decisions on antibiotic duration, but we accept that CRP may be measured outside of the study protocol if the treating clinician believes that this is an important part of a patient's care not related to decisions about antibiotic duration. Any non-trial use of CRP in standard care will be recorded in the Case Report Form and will be monitored at each site by the research team.

The non-trial use of PCT during the intervention phase presents a challenge - it has the potential to influence antibiotic duration as centres will be using similar stop rules to those in the trial protocol and that are acknowledged internationally. Maintaining equipoise for the purposes of this trial involves avoiding PCT use up to 28-days post randomisation, as this could impact on the primary outcome (duration of antibiotics to 28 days). Any non-trial use of PCT will be recorded as a protocol deviation and will be monitored at each site by the research team.

2.10 Blinding

2.10.1 Methods for ensuring blinding

Following patient recruitment, randomisation will be initiated by the local investigator team using a 24-hour trial web-based system and group assignment will be available to the laboratory service only through this web-based system. Group allocation will be concealed from the patient and their relatives, the treating clinical teams and the local research staff. A research blood sample (at least 2ml) will be collected from each recruited patient, including standard care only (control group) and standard care plus biomarker-guidance (intervention groups), to maintain group concealment. Research blood samples will be allocated a unique research study number and will be transported to the laboratory. The research number will not reveal the identity of the patient to laboratory staff. A sample will be collected and transported to the laboratory each day for every recruited patient (control and intervention groups) until antibiotics are discontinued by the clinical team responsible for patient care.

Clinical biochemistry laboratory results are delivered to care teams throughout the NHS via laboratory-based electronic systems. For research studies, a 'dummy patient' will be set up in a laboratory electronic request system that allows requesting and reporting of, in this case, CRP and PCT tests, using the unique research number and removes the possibility of results entering routine patient care. The trial website will be the route for routine reporting of research laboratory results and web-based automated advice will be available to the clinical research teams on a daily basis for each patient to generate the daily written standardised advice for the clinicians responsible for patient care as described in Table 1.

Biomarker values will not be reported back to routine clinical service.

2.10.2 Un-blinding the trial

Group allocation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

2.11 Internal pilot study

The main trial will be preceded by an internal pilot study running for 9 months from when the first patient is randomised and will follow the same processes described in the main trial. The pilot will take place in up to 12 sites chosen to reflect those centres that will take part in the main trial. The pilot will be used to assess recruitment rates, protocol compliance and data collection and aims to recruit about 9% of the total study sample size (19).

We will audit (a) screening; (b) recruitment; (c) reasons for exclusion; (d) protocol adherence and (e) ensure that the protocol and training received is implemented into practice by using data recorded in screening logs, Case Report Forms and during site visits. Recruitment feasibility criteria will be based on the planned recruitment rate from the date the site started. Protocol adherence will be captured using specific data recorded in the Case Report Forms of adherence to biomarker-guided advice on antibiotic discontinuation – and reasons for non-adherence will be documented if it occurs. Progression and success criteria (from pilot to main study) will be assessed on both (a) recruitment and (b) protocol adherence.

Success criteria for recruitment are as follows:
The recruitment period for each site is measured from the date the first patient is recruited up to the pilot end date.

A) Recruitment rate ≥75%:
   This will be calculated as pilot sites recruiting 3 or more patients per month on average.
   RECOMMENDATION: progress to main trial following a review of screening logs and protocol. Barriers to recruitment will be addressed and additional sites may be opened.

B) Recruitment rate <75%:
   This will be calculated as pilot sites recruiting less than 3 patients per month on average.
   RECOMMENDATION: If the average recruitment rate is ≥2 but less than 3 patients per month then progress to main trial with additional sites being recruited as well as a screening log and protocol review.
   However, if the recruitment rate observed at the end of pilot is <2 per month then the potential justifications of continuing the trial will be presented to the TSC in association with the HTA secretariat to recommend whether to continue with the main trial.

In addition, we will use similar success criteria for protocol adherence to guide progression to the main trial. If evaluable data required to measure the primary outcomes of superiority and non-inferiority is <95% we will develop additional training for sites on data collection and case report form (CRF) completion.

At the end of the pilot phase the Data Monitoring Committee (DMC) will review progress against target recruitment and protocol adherence outcomes. They will also review the non-trial use of CRP and PCT measurements for each of the trial groups and will assess evidence for likely group

separation in the main trial in terms of the primary efficacy (antibiotic duration) and safety (28-day all-cause mortality) outcomes. In conjunction with the independent Trial Steering Committee (TSC), investigators will develop guidance for the DMC on trial progression from the internal pilot phase to include the criteria described above.

2.12 End of trial

The trial will end when all participants have completed 90-day follow-up and the trial database is locked.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

2.13 RISC-Sepsis

The primary objective of RISC-sepsis will be to determine differences in duration of antibiotics during the ADAPT-sepsis biomarker-guided antibiotic phase, antibiotic use at 28-days, hospital-acquired infection, and length of ICU and hospital stay between patients with sepsis-induced immunosuppression and patients without. The secondary objective will be to monitor cell surface markers of leucocyte function during the time-course of the ADAPT-sepsis biomarker-guided antibiotic phase.

A sample size of 180 patients will be recruited from a sub-set of participating ADAPT-sepsis sites. Blood will be sampled for RISC-sepsis only during the ADAPT-sepsis intervention period. The schedule of blood sampling for RISC-sepsis is illustrated below:

Visit day	1	2	3	4	5	6	7	8-28
Screening, randomisation	✓							
ADAPT-sepsis sampling	Baseline	Biomarker-guided antibiotic discontinuation. Daily sampling while receiving antibiotics						
RISC-sepsis: sample for flow cytometry and serum biomarker measurement	✓		✓		✓		✓	
RISC-sepsis: Sample for WCC RNA measurement	✓				✓			

Table 2: Blood sampling schedule.

Blood will be sampled at these time points for measurement of leucocyte cell surface markers by flow cytometry, serum measurement of biomarkers, and leucocyte RNA. The sampling period for RISC-sepsis will extend to day 7 or until the ADAPT-sepsis sampling period ends, whichever occurs first. A maximum of 20 mls of extra blood will be collected per RISC-sepsis research sample taken.

Measurements will include, but not be limited to, monocyte HLA-DR, neutrophil CD88, programmed cell death (PD)-1, percentage regulatory T cells, PCT, CRP and leucocyte RNA. Samples will be collected and stored according to SOPs. Samples for measurement by flow cytometry and serum biomarkers will be transferred to Newcastle University and leucocyte RNA samples will be transferred to Imperial College London.

Biological measures will be linked to trial outcome measures including duration of antibiotics during the ADAPT-sepsis biomarker-guide phase, antibiotic use at 28 days, occurrence of hospital-acquired infection and length of ICU and hospital stay.

3 PATIENT VISIT SCHEDULE AND FOLLOW-UP

3.1 Schedule of delivery of intervention and data collection

Visit day	1	2	3	4	5	6	7	8-28
Screening	✓							
Informed Consent (Patient consent/ Consultee /Guardian/Welfare Attorney/ Retrospective Patient Information & consent)	Patient / Consultee (Guardian/Welfare Attorney) Opinion/consent will be obtained initially. Retrospective patient consent will be obtained when/if the patient has recovered mental capacity during acute hospital care.							
Medical history and baseline characteristics	✓							
Inclusion/exclusion criteria	✓							
Randomisation	✓							
Baseline research blood sample	✓							
Intervention		Biomarker-guided antibiotic discontinuation						
SOFA score	✓		✓				✓	
Adverse events (see section 4.1.1)		✓	✓	✓	✓	✓	✓	✓
Follow-up								
Daily collection of clinical information, infection status, antibiotic use and care environment	✓	✓	✓	✓	✓	✓	✓	✓
Final visit	On day of hospital discharge *If the patient is discharged to another hospital or to the community within 28 days following randomisation, the local research team will contact the patient and their treating health care professional (hospital physician or General Practitioner) to collect outstanding information about the stated primary and secondary outcomes.*							

Table 3 Schedule of delivery of intervention and data collection

Data collection will include:

Baseline characteristics data

- Patient identifier, NHS number, age and gender;
- Inclusion and exclusion criteria;
- Sepsis severity;
- Admission diagnosis;
- Cause and site of infection including diagnostic evidence;
- APACHE II and SOFA score
- First 24-hour sepsis care bundle treatments and interventions, including antibiotics.

Data collected daily from randomisation on/until hospital discharge

Up to 28-days post randomisation:

- Duration of antibiotic use (days in 24 hour periods from randomisation);
- Survival status;
- Re-lapse/recurrence and super-infection/new infection rates;
- Unscheduled re-admission or care escalation;
- Name and dose of antibiotics (expressed as Defined Daily Dose);
- Protocol adherence (including any use of CRP and PCT outside of trial protocol)
- Day 3 and 7 SOFA scores;
- The length of critical care admission;
- Time 'fit' for hospital discharge;
- The length of hospital stay;
- Suspected clinically relevant antibiotic related adverse reactions;
- Serious adverse events.

Up to 90-days post randomisation:

- All-cause mortality up to 90 days.

Data collected after hospital discharge

Up to 28-days post randomisation:

- Duration of antibiotic use (in days from randomisation);
- Survival status (up to 28 days);
- Re-lapse/recurrence or super-infection/new infection rates (from day 1 to 28);
- Unscheduled re-admission or care escalation;
- Name and dose of antibiotics (expressed as Defined Daily Dose);
- Suspected clinically relevant antibiotic related adverse reactions;
- Serious adverse events.

Up to 90-days post randomisation:

- All-cause mortality up to 90 days.

3.2 Long term follow-up assessments

Patients will be followed up to ascertain all-cause mortality rates at 90 days using NHS Digital, the Intensive Care National Audit and Research Centre and equivalent NHS data linkage in Scotland.

4 ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An AE is: "Any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research, which does not necessarily have a causal relationship with the research".

The duration of antibiotic treatments for sepsis is the primary objective of this study. Therefore, any clinically relevant antibiotic related reactions occurring from the time of randomisation until 28 days will be recorded as pre-defined trial outcome. Events will be deemed clinically relevant and related if antibiotic treatment has been changed due to a suspected reaction to the previous antibiotic. The following clinically relevant antibiotic related events will be recorded in the Case Report Forms and do not need separate recording as adverse events:

- Anaphylaxis
- Gastrointestinal
- Haematological
- Hepatobiliary
- Renal
- Neurological
- Dermatological
- Cardiac
- Muscular
- Clostridium Difficile diarrhoeal infection
- Multi-drug resistant organism
- Other (clinician's discretion)

4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition (i.e. if they jeopardise the subject or require an intervention to prevent one of the above.)

Exemptions to SAE reporting

The primary events of infection and sepsis are classified as pre-existing conditions in the trial. As such, the occurrence or expected progression of infection and sepsis-related events, including death, will occur. These events will be recorded in the medical records and assessed in the same way as SAEs. However, they are not usually recorded as SAEs, unless they are thought to be related to participant involvement in the trial. Specifically, clinical outcomes from infection and sepsis, and outcomes related to the interventions of biomarker-guided decision on antibiotic duration,

including clinically relevant antibiotic related reactions listed above in 4.1.1, are exempt from adverse event reporting. The following events will be collected as outcomes and will be recorded in the relevant CRF so do not need to be reported as SAEs:

- All-cause mortality at 28 and 90 days post randomisation (unless the site investigator feels the death is related to the participation in the trial) Cardiovascular failure, including the need for vasopressors / inotropes
- Respiratory failure, including mechanical ventilation and acute lung injury
- Hepatic failure
- Renal failure, including the need for renal replacement therapy
- Haematological / coagulation failure, including thrombocytopaenia
- Neurological failure
- Unscheduled care escalation/re-admission
- Infection relapse/recurrence requiring further antibiotic treatment
- Super-infection defined as new infection at a different anatomical site
- Suspected antibiotic adverse reactions

Clinical decisions about antibiotic initiation and drug choice are not the object of this trial and will be at the clinical judgement of the treating clinicians in each of the three study groups.

Reporting SAEs

All **SAEs** occurring from the time of randomisation until 28 days must be recorded on the SAE Form and emailed (see below) to the study coordinating centre **within 24 hours** of the research staff becoming aware of the event.

For each **SAE** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator.

Any change of condition or other follow-up information should be emailed to the study coordinating centre as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.
SAEs will be reported using the SAE form in the participant's CRF. The Principal Investigator in each centre must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event.

The SAE form should be completed and anonymised, and emailed to Warwick CTU: WCTUQA@warwick.ac.uk and copied to the trial office email(adaptsepsistrial@warwick.ac.uk).

The trial manager/trial coordinator will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected

SAEs to the sponsor and REC within required timelines. The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

Where an SAE is assessed as causally related to the intervention by either the CI or site investigator, WCTU will undertake an assessment of expectedness. If the resulting related SAE is unexpected, this will be reported to the REC within 15 days.

Relationship to trial medication	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

4.2 Adverse event responsibilities

4.2.1 Principal Investigator (PI)

Checking for AEs when participants during trial and 28-day follow-up.

1. Using medical judgement in assigning seriousness and causality
2. Ensuring that all SAEs are recorded and reported to the trial coordinating centre within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with the trial coordinating centre if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs are recorded and reported to the trial coordinating centre in line with the requirements of the protocol.

4.2.2 Chief Investigator (CI) / delegate or independent clinical reviewer

1. Clinical oversight of the safety of patients participating in the trial.
2. Using medical judgement in assigning causality assessments to SAEs (independently of the site causality assessment)
3. Assigning expectedness to related SAEs.
4. Immediate review of all related and unexpected SAEs

5. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Production and submission of annual reports to the relevant REC.

4.2.3 Sponsor

The Sponsor (the University of Manchester) has delegated full trial delivery responsibilities to Warwick Clinical Trials Unit but will retain overarching responsibility for:

1. Central data collection and verification of AEs, and SAEs, according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
5. Notifying Investigators of related and unexpected SAEs that occur within the trial.
6. The un-blinding of a participant for the purpose of expedited reporting.

4.2.4 Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

4.2.5 Data Monitoring Committee (DMC)

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.3 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5 DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 2018 Data Protection Act. Participants will be identified using a unique trial number only.

5.1 Data collection and management

The case report forms (CRFs) will be designed by the Trial Coordinator in conjunction with the Chief Investigator and Statistician.

All data for an individual participant will be collected by each Principal Investigator or their delegated nominees and recorded in the CRF. Participant identification in the CRF will be through their unique Participant Study Number (TNO) allocated at the time of randomisation and initials. Data will be collected daily from the time the patient is considered for entry into the trial through to their discharge from hospital. In the event that a participant is transferred to another hospital, the site research team will liaise with the receiving hospital to ensure complete data collection. In the event

that a participant is discharged into the community prior to day 28, the site research team will utilise the following hierarchy in order to collect the day 28 follow up data:

1. Access NHS electronic patient data if that option is available and in routine use in the treating hospital.
2. If the treating hospital does not have facilities to access NHS electronic patient records , site staff will liaise with the participants GP using the GP letter and follow-up telephone contact
3. If data collection does not result from options 1 and 2, site staff may contact the participant or their nominated contact in order to obtain the data. If using option 3 site staff should perform a mortality check ahead of making contact.

Data will be collected either by using a web-based secure remote data capture system or in paper form. Once a participant has been discharged from hospital and all data entered into the CRF, the original of each form will be returned to the Study Coordinating Centre. A copy of the CRF will be retained at the recruiting centre. Submitted data will be reviewed for completeness and entered onto a secure, backed-up bespoke database. Due care will be taken to ensure data safety and integrity, and compliance with all relevant UK regulations.

To ensure accurate, complete and reliable data, the Study Coordinating Centre will do the following:

- Provide instructional material to the trial site(s)
- Provide support to the site PI in running a site initiation meeting. This session will give instructions on the protocol, the completion of Case Report Forms and study procedures
- Make periodic visits to the study sites
- Be available for consultation and stay in contact with the study site personnel by mail, telephone.
- Review and evaluate Case Report Form (CRF) data, source data (as required), detect errors in data collection and request data clarification.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmers and appropriate trial staff.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.4 Data access and quality assurance

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Any paper data forms will be stored in a secure location which is restricted to research team access. Electronic data will be stored in a secure area of the computer with access restricted to staff working on the trial. All databases containing identifiable information will be password protected. Any data that are transferred out of the secure environment (for example for statistical analysis, ICNARC, HES) will adhere to our unit SOPs.

Direct access to source data held in participating sites will be required for monitoring / quality assurance purposes throughout the trial. Monitoring will be conducted by members of the trial team only and will not be subcontracted to a third party.

5.5 Data Shared with Third Parties

Data will be shared between the project and NHS Digital for the purposes of data linkage to obtain mortality data and hospital episode statistics. This will include sharing NHS number and date of birth information. Additionally, data will be shared for similar linkage purposes with ICNARC. Health Economic analysis will be conducted in collaboration with Sheffield University. Equivalent data sharing agreements will be put in place between the project and NHS Scotland and Cardiff & Vale University Health Board. Specifically, in Scotland, data will be shared between the trial and the electronic Data Research and Innovation Service, a part of the Information Services Division of National Services NHS Scotland, for the purposes of data linkage to obtain mortality data, intensive care audit data (from the Scottish Intensive Care Society Audit Group database) and acute hospital statistics (from Scottish Morbidity Record 01). This will include sharing Community Health Index number and other fields required by electronic Data Research and Innovation Service for linkage. All data sharing will be subject to appropriate contractual and governance requirements, including approval from Scottish Intensive Care Society Audit Group database steering group and the Public Benefit and Privacy Panel for Health & Social Care.

All data sharing will be subject to appropriate contractual and governance requirements.

5.6 Archiving

Trial documentation and data will be archived for at least fifteen years after completion of the trial. Trial Master File and associated data will be archived by WCTU, trial data generated at study sites will be archived according to local policy.

6 STATISTICAL ANALYSIS

6.1 Power and sample size

For our proposed trial, clinical effectiveness (antibiotic duration) will have to demonstrate benefit while the safety outcome (28-day all-cause mortality) is maintained in order to inform a meaningful change in practice. Therefore, our primary effectiveness outcome (antibiotic duration) will not provide all the information as regards the treatment effect. Safety is paramount - only if an intervention arm is not worse than the control (standard care only) will it be acceptable.

A total sample size of 2760 would be able to detect both a mean of 1-day (0.93 days to be precise) reduction in antibiotic duration (using a mean antibiotic duration of 7 days, a pooled standard deviation of 6 days, 90% power, a significance level of 5%, with a 5% withdrawals rate) and a non-inferiority safety margin of 5.4% (using a 1-sided significance level of 2.5%, 90% power and 5% withdrawal rate) assuming 28-day mortality is 15% in both arms.

This total sample size was informed by the following evidence:

- Consensus International guidelines for sepsis management recommend antibiotic treatment duration of 7-10 days (7), with UK guidance from Public Health England at the lower end of this range – 7 days (10). Jong and colleagues (20) derived a standard deviation of 6-day duration of antibiotic use from six randomised controlled trials and prospective studies with a mean treatment duration of 8-days.

- Data from the NIHR HTA commissioned systematic review (13) of biomarker-guided antibiotic treatment duration for sepsis illustrated, from the best available evidence, a mean difference between standard care and PCT biomarker guided therapy of 1.2 (95%CI: 1.07, 1.33) days of antibiotic use for sepsis and a mean difference of 3.85 (95%CI: 6.78, 0.92) days when including a broader range of studies in critically ill patients at high risk of severe sepsis. Currently, there are estimated to be at least 200,000 cases of sepsis/annum across the UK (16). Therefore, with an average antibiotic saving of at least 1.2 days for each patient with sepsis across the whole NHS (likely broad-spectrum agents) could produce a meaningful change in practice in terms of antibiotic exposure which, according to NICE, would also be cost-saving and more effective (16).

- The NIHR HTA systematic review (13) detailed all-cause mortality at 28-days ranging from 12.5%-24.0%, primarily in critical care unit settings. Following the implementation of international guidelines for management of sepsis, there is observational evidence to suggest that mortality rates are declining (4). For this reason, we estimate the mortality rate for sepsis in the standard care arm will be 15%.

- Loss to follow up in UK acute care trials (21-23) is often low (<3%). A number of studies report no withdrawals internationally (24-26), whereas others report a rate of 1%-5% withdrawals (27, 28). Taking the most conservative rate, we have powered our study for a 5% withdrawal rate.

Our proposed margins of non-inferiority (NI) is in keeping with Sorbello's suggested standard absolute NI margin of 7% with respect to all-cause mortality for clinical trials that assess antibiotic drug efficacy in critically ill patients (29). In addition, non-inferiority margins for our primary safety outcome (28-day all-cause mortality) are improvements on those set by studies contained within current NICE guidance on PCT-guided antibiotic treatment duration for sepsis (16). For instance, in two of the largest interventional studies, Jong (20) and Bouadma (28) set their absolute NI mortality margins at 8% and 10% respectively. Furthermore, based in these historical non-inferiority data and evidence from secondary clinical outcomes from reviewed trials, NICE guidance on PCT-guided antibiotic discontinuation clearly states that it is unlikely to result in worse clinical outcomes compared with standard clinical practice alone (16). We believe, therefore, that delivering our proposed trial in the NHS will provide more robust evidence on effectiveness and safety for biomarker-guided antibiotic treatment duration than is currently available from international trials.

6.2 Statistical analysis

6.2.1 Planned recruitment rate

We aim to recruit 2760 patients, this includes an internal pilot study recruiting the first 249 patients from 12 sites

6.2.2 Statistical analysis plan

Primary outcome analysis

The primary effectiveness analyses will assess whether any of the biomarker interventions are better than standard care. The primary analysis approach for the duration of antibiotics will be intention-to-treat (ITT). ITT analysis will consist of all randomised patients and will assess the effect of treatment assignment. For the ITT analysis, linear mixed effects regression models will be fitted with a random effect for centre to estimate the effect of treatment having adjusted for any important predictors of the primary outcome. In this trial, participants may die before antibiotic therapy is discontinued. In such cases the outcome is undefined and is referred to as 'truncated by death'. A crude comparison between the survivors on each treatment arm may give rise to biased outcome comparisons. Therefore we will consider undertaking some sensitivity analyses to estimate treatment effect having accounted for the deaths.

The primary safety outcome (28-day all-cause mortality) is based on assessing non-inferiority and we specify the null hypothesis that the biomarker interventions are much worse compared with standard-of-care. The primary safety outcome will be analysed using mixed effects logistic regression models, with adjustments for important predictors. The unadjusted and adjusted proportion estimates and the 95% confidence intervals will be compared with the non-inferiority margin to accept/reject the null hypothesis.

Secondary outcome analysis

Secondary outcomes will be assessed using an ITT approach. Continuous secondary outcomes will be analysed in the same way to the primary outcome and the categorical outcomes will be assessed using mixed effects logistic regression models. Time-to-event outcomes will be analysed using Cox proportional hazards models and reported as hazard ratios with a 95% confidence interval. A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician and approved by the DMC prior to any analysis.

6.3 Subgroup analyses

Exploratory analysis will be reported using 99% confidence intervals. Logistic regression will be used with interaction terms (treatment group by sub-group) for the following sub-groups selected from a recent NCEPOD report (2) about the management of infection causing sepsis in the NHS.

- Community-acquired pneumonia (CAP);
- Hospital-acquired pneumonia (HAP);
- Urinary tract infection (UTI);
- Intra-abdominal infection;
- Infection with positive blood culture.

In addition, community acquired, hospital acquired infections and SARS-Cov-2 will be analysed as subgroups.

From the NCEPOD report on sepsis (2), including all community and hospital acquired infections together, respiratory tract infections accounted for 43% of sepsis cases, urinary tract 24%, intra-abdominal 18%, and 16% of sepsis patients had a positive blood culture, indicating the likely range of infection sources that will be included in our proposed comprehensive trial in sepsis.

6.4 Interim analysis and criteria for premature termination of the trial

The timing and frequency of the interim analyses will be discussed and agreed with the DMC members and will include an introduction meeting at the start of the project and a meeting following the internal pilot. In the light of the evidence provided within recent NICE guidance on the adequate safety biomarker-guided antibiotic therapy and that treating clinicians make the final decision on patient therapies, it is anticipated that no more than one formal interim analysis will be required during the course of the main study. The DMC will monitor safety regularly throughout the study and will make recommendations to the trial steering group (TSC) about stopping early if required.

6.5 Health Economic Evaluation

Decision-analysis modelling will be used to estimate the expected costs incurred and patient outcomes from the two interventions and the control arm. The model would be populated with data directly taken from the proposed trial and would include key outcomes such as: rates of mortality; costs associated with length of stay for the index hospitalisation, including escalation of care; costs associated with readmission; and costs associated with antibiotic use. Whilst an immediate estimate of the costs of the two interventions and the control can be directly calculated from the trial a mathematical model is required as the data captured in the trial is of an insufficient duration to capture the long-term consequences of avoided mortality or morbidity. The decision analysis model would extrapolate from the outcomes for each arm at the end of the study to estimate the quality adjusted life years (QALYs) conditional on the proportion of patients who are alive, and of these, the proportion that would have reduced health-related quality of life in the future. Estimates of survival rates (which may be reduced due to prior sepsis) and of the disutility associated with observed adverse events in the trial would be sourced from peer-reviewed literature. Similarly, any costs associated with long-term disabilities would be identified and included within the decision-analysis model.

The mathematical model would allow an explicit evaluation of the uncertainty in any conclusions drawn from the trial and allow value of information analyses to be performed to indicate if further research would be deemed as value for money.

At present the precise modelling methodology to be implemented has not been determined. This decision will be made in conjunction with clinical experts and having assessed the available data. For reassurance, it is stated that the research team are highly familiar with cohort Markova models and decision trees, and have published using more advanced methods such as individual patient modelling (31), discrete event simulation (32), area under the curve analyses (33) and meta-modelling (34).

6.6 RISC-Sepsis

We will assess the time it takes for the patients to stop antibiotics during the ADAPT-sepsis biomarker-guided antibiotic phase for patients who are ‘immunosuppressed’ and those who are not. We will present summary statistics and assess the distribution of the outcome. Depending on the distribution, the number of antibiotic days will be compared between groups using either the geometric mean or the arithmetic mean obtained from linear regression models and adjusted for confounding variables. In addition, each of the cellular markers will also be assessed as a continuous outcome. We will look at the change from baseline to time-point 1, time-point 1 to time-point 2,

time-point 2 to time-point 3 and time-point 3 to time-point 4, for each cellular marker and assess the correlation between the change and the number of days on antibiotics using Spearman's correlation coefficient. We will summarise these changes using summary statistics (mean, standard deviation, median, range) and one sample t-tests will be used to assess the change.

We will summarise the primary trial outcome of 28-day antibiotics and secondary trial outcomes (hospital-acquired infections and length of ICU and hospital stay) for patients who were 'immunosuppressed', compared to those 'non-immunosuppressed'. We will use similar methods as stated above. For categorical outcomes, we will use logistic regression models. We will describe the difference between the groups using p-values, point estimates and 95% confidence intervals.
We will look for differences in PCT and CRP levels (point estimate and 95% confidence interval) between periods when patients are 'immunosuppressed' and when 'non-immunosuppressed'. This will be performed by identifying the time interval each of the patients were immunosuppressed and within this time interval, we will assess their PCT/CRP levels (averaged over time for each patient). We will then make a comparison with the time periods when the same patient was not immunosuppressed. We will use linear regression models to make a comparison of the two states within patients, with a random effect as the patient (to account for within patient level). In order to correct for any bias, we will adjust for confounders.

We will assess the change in immunosuppression markers over time and compare this with change in PCT and CRP biomarkers. To standardise the scaling, we will use percentage change between time-points.

Sub-group analyses:
Exploratory analysis will be reported using 95% confidence intervals. Regression models will be used with interaction terms ('immunosuppression' by sub-group) using the number of days on antibiotics for the following sub-groups:

1. Medical *versus* surgical
2. Trauma *versus* non-trauma
3. Community-acquired infection *versus* hospital-acquired infection
4. Infection site: community-acquired pneumonia; hospital-acquired pneumonia; urinary tract infection; intra-abdominal infection; positive blood culture.

7 TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The trial will be conducted in full conformity with the Declaration of Helsinki according to its 1996 version. The University of Manchester will act as trial Sponsor and has delegated all trial delivery responsibilities to Warwick Clinical Trials Unit. The study will be conducted in accordance with the Protocol, Good Clinical Practice, Warwick Clinical Trials Unit Standard Operating Procedures (WCTU SOPs) and national regulatory requirements and the provisions of relevant ethics committees.

7.2 Ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations.

Recruitment may not start until the Sponsor has given greenlight approval. Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D agreement is received by Warwick Clinical Trials Unit acting on behalf of the Sponsor.

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, analyses) will be managed by WCTU trial team and communicated by them (following approval by the Sponsor and funder) to relevant parties i.e. investigators, RECs, participants, NHS Trusts, trial registries, journals. Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC will be notified of the end of the trial (whether at planned time or prematurely).

The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

7.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register.

7.4 Notification of serious breaches to GCP and/or trial protocol

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

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The Sponsor will notify the approving ethical committees in writing of any serious breach of:

- the conditions and principles of GCP in connection with that trial; or
- the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Manchester provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Administration

The trial co-ordination will be based at Warwick Clinical Trials Unit (WCTU), University of Warwick.

7.7 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate. A Core Trial Management Group will meet monthly and a Full Trial Management Group, incorporating all of the listed co-applicants, will meet approximately 4 times per year.

7.8 Trial Steering Committee (TSC)

The trial will be guided independently by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.
The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial.

7.9 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet after the first 249 patients have been recruited (the Internal pilot study) and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated. DMC meetings will also be attended by the Chief Investigator and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

7.10 Essential Documentation

A Trial Master File will be set up according to Warwick Clinical Trials Unit Standard Operating Procedures and held securely at the trial coordinating centre.
The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7.11 Financial Support

The trial has been funded as commissioned research by the NIHR HTA Programme (15/99/02).

8. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and Sponsor based on the trial risk assessment and will include on site monitoring. Where on site

monitoring is not possible (i.e. due to the COVID-19 pandemic) monitoring will be performed remotely.

8.1 Training

Principal Investigators, site research teams and an appointed laboratory lead as listed on the delegation log and WCTU administration staff will be required to undergo GCP training. Principal Investigators will be required to provide a CV to WCTU.

8.2 Visits to Sites

Prior to site activation a site initiation visit/teleconference/videoconference will be performed in order to provide training to the site team on the conduct of the trial.

Sites will be expected to assist the sponsor in monitoring the study. This will include hosting site visits and providing information for remote monitoring. This will include providing direct access to source data/documents where required. Investigator Site Files will be checked to ensure documents are up to date at least once during the trial.

Monitoring visits will be conducted in a supportive manner with the objective of supporting centres in delivering the study safely and in accordance with the principles of GCP.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

The applicants have worked with the Intensive Care Society's Patients and Relative Committee (ICSPRC) which includes the ICU Support Teams for Ex-Patients (ICUSteps). These groups include patients and relatives who have experienced sepsis and acute hospital care, providing crucial insights for our proposed study and its acceptability for patients. Specific work includes: developing a study protocol to offer participation to a wide range of hospitalised adults with sepsis across the UK; ICSPRC chair (Keith Young), as co-applicant, has contributed to protocol development and developing our PPI study plan; co-writing Plain English Summary; and help with developing connectivity with relevant government advisory groups (notably the Advisory Committee on Antimicrobial Resistance & HAI). Mr Young has also contributed to, and approved, the final trial design and he will sit on the Trial Management Group (TMG), with specific responsibility for ensuring study documentation is accessible to a public audience. Additionally, there will be public representation on the Trial Steering Committee (TSC). To ensure broader engagement, a PPI collaboration will be formed, with links to the TMG. This will be a two-way process, to ensure the research team benefit from understanding public perception on sepsis and outputs are communicated effectively to the public.

10. DISSEMINATION AND PUBLICATION

All publications and presentations relating to the study will be authorised by the Trial Management Group. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (35, 36) and the template for intervention description and replication (TIDieR) checklist and guide (37).

The success of the trial depends on the collaboration of doctors, nurses, laboratory scientists and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

We will publish our trial protocol and statistical analysis plan to ensure transparency in our methodology. The study findings will be presented at national and international meetings with abstracts on-line, with wide social media coverage so that results and their implications quickly reach all of the relevant UK clinical communities. This will be facilitated by our investigator group which includes key individuals linked to societies, professional bodies, the Department of Health and patient/relative groups across a wide range of responsibilities relevant to the planning of the management of sepsis, laboratory chemistry, antibiotic stewardship and antimicrobial resistance in the NHS. In accordance with NIHR open access policies we will publish the clinical findings of the trial as well as a paper describing the cost-effectiveness in the NHS setting in high quality peer-reviewed open access (via PubMed) journals. A final report will also be published in the NIHR HTA journal. We will actively promote the findings of the study to journal editors, sepsis care and antimicrobial stewardship opinion leaders to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines.

NICE issued guidelines for PCT monitoring of sepsis in 2015 (16) and encouraged clinicians to enter patients into future NHS clinical trials aimed at testing biomarker-guided antibiotic discontinuation protocols for sepsis. We have planned our trial to address NICE's recommendations so that subsequent results will inform their future guidance on sepsis. The trial methods we have proposed would ensure that publications from the trial would be given a good rating by an assessment group using the Cochrane risk of bias score (38). We will inform NHS managers and commissioners if the study supports a change of practice.

A lay person's summary will be sent to local and national patient support and liaison groups notably the ICSPRC and ICUSteps. A report of the study findings will be sent to the INVOLVE registry. This is an open-access database which registers research health care projects involving members of the public as partners in the research process. Following peer reviewed publication, appropriate key Publication findings will be communicated through press releases led by the NIHR in partnership with the trial host institutions.

10.1 Intellectual Property (IP)

It is not expected that any existing or new commercial IP will be improved or produced during the conduct of this Trial. The TSC and CI will monitor throughout the Trial. It is expected that the results of this study will form Foreground IP that will become part of, for example, the evidence base for future clinical practice and guideline development by organisations such NICE.

Any potential new IP will be discussed amongst all relevant parties with reference to the NIHR policy on IP and according to collaboration and data sharing agreements. Support for identification,

protection, management and exploitation of IP will be provided through Salford Royals partnership with Trustech for the NHS and in discussion with UMIP for the University of Manchester. IP sharing will adhere to existing sharing agreements within the Manchester Academic Health Science Centre partnership - providing the main vehicle for interaction between the University of Manchester and partner NHS teaching hospitals. Collaboration Agreements will bind collaborators under the terms of the NIHR funding agreement for future use of Foreground IP for non-commercial research, teaching and clinical purposes to maximise value to subsequent patient benefit.

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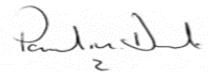
SIGNATURE PAGE - CHIEF INVESTIGATOR

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Signed: 

Professor Paul Dark,
Division of Infection, Immunity and Respiratory Medicine,
University of Manchester

Date: 22/02/2022

SIGNATURE PAGE – Warwick Clinical Trials Unit Lead

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Signed: 

Professor Gavin Perkins,
Professor of Critical Care Medicine,
University of Warwick

Date: 21/02/2022

SIGNATURE PAGE - SPONSOR

The signature of the below constitutes agreement of this protocol by the signatory.

Signed: 

Dr Mohammed Zubair,
Research Governance Ethics & Integrity Manager,
University of Manchester

Date: 18/01/2022

SIGNATURE PAGE - STATISTICIAN

The signature of the below constitutes agreement of this protocol by the signatory.

Signed: _____

Professor Ranjit Lall,
Warwick Clinical Trials Unit (WCTU),
Warwick Medical School

Date: 17/01/2022

SIGNATURE PAGE - INVESTIGATOR

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Biom**A**rker-guided **D**uration of **A**ntibiotic treatment in hospitalised **P**a**T**ients with suspected **Sepsis**: the **ADAPT-Sepsis** Trial.

Protocol Number: _____

Address of Institution: _____

_____

_____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____