# ARREST

# Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia: a multi-centre, randomised, blinded, placebo controlled trial

## United Kingdom Clinical Infection Research Group (UKCIRG)

**Version:** 5.0

**Date:** 01 October 2015

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| **ISRCTN #:** | **37666216** |
| **EUDRACT #:** | **2012-000344-10** |
| **CTA #:** | **00316/0243/001** |
| **MREC #:** | **12/LO/0637** |

Authorised by:

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|---|---|
| **Name:** | **Professor Guy Thwaites** |
| **Role:** | **Chief Investigator** |
| Signature: |  |
| Date: | 01 October 2015 |

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| **Name:** | **Professor A. Sarah Walker** |
| **Role:** | **Trial Statistician** |
| Signature: |  |
| Date: | 01 October 2015 |

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|---|---|
| **Name:** | **Dr Adrian Martineau** |
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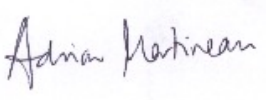
| Signature: |  |
| Date: | 01 October 2015 |

# GENERAL INFORMATION

This document was constructed using the MRC CTU Protocol Template Version 4.0. It describes the ARREST trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the ARREST trial team, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

## COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC [where applicable]) and applicable national regulations.

## SPONSOR

The MRC is the trial sponsor and has delegated responsibility for the overall management of the ARREST trial to the MRC CTU at UCL. Queries relating to MRC sponsorship of this trial should be addressed to the Director, Regional Centre London, Aviation House, 125 Kingsway, London WC2B 6NH, UK or via the trial team.

## FUNDING

The ARREST trial is funded by the Health Technology Assessment (HTA) Programme of the National Institutes of Health Research (NIHR) (10/104/25).

## AUTHORISATIONS AND APPROVALS

This trial will be submitted for Research Ethics Committee (REC) approval through the UK National Research Ethics Service and, therefore, after approval will be submitted for inclusion as part of the London (South) Comprehensive Clinical Research Network portfolio.

## TRIAL REGISTRATION

This trial has been registered with the International Clinical Trials Register, where it is identified as 37666216.

**RANDOMISATIONS**
To randomise, please go to https://macro.ctu.mrc.ac.uk/macro/
24hrs a day, 7 days a week.
If the ARREST database is not available, please complete the Emergency Paper CRF and fax to **020 7670 4817** or email to **mrcctu.arrest@ucl.ac.uk**

**SAE REPORTING**
Within 24 hours of becoming aware of an SAE, please go to https://macro.ctu.mrc.ac.uk/macro/ to complete the SAE eCRF, and email the MRC CTU at UCL to notify them on: **mrcctu.arrest@ucl.ac.uk**
If the ARREST database is not available, please complete the Emergency Paper CRF and fax to **020 7670 4817** or email to **mrcctu.arrest@ucl.ac.uk**

## TRIAL ADMINISTRATION

Please direct all queries to the ARREST Trial Manager at the MRC Clinical Trials Unit at UCL in the first instance; clinical queries will be passed to the Chief Investigator via the Trial Manager. For emergency unblinding, please call the Chief Investigator on 07818 040689. If the Chief Investigator is unavailable please call MRC CTU at UCL on 07746 795024. For more details on unblinding and emergency unblinding please see Section 5.5 - Unblinding p34.

### COORDINATING SITE

| | | |
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### MRC CTU AT UCL STAFF

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### CO-INVESTIGATORS

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For full details of all trial committees, please see Appendix I - Trial Steering Committee and Data Monitoring Committee Membership, p80.

## SUMMARY OF TRIAL

| SUMMARY INFORMATION TYPE | SUMMARY DETAILS |
|---|---|
| **ACRONYM** | ARREST |
| **Long Title of Trial** | **A**djunctive **R**ifampicin to **R**educe **E**arly mortality from **ST**aphylococcus aureus bacteraemia: a multi-centre, randomised, blinded, placebo controlled trial |
| **Version** | 5.0 |
| **Date** | 01 October 2015 |
| **ISRCTN #** | 37666216 |
| **EudraCT #** | 2012-000344-10 |
| **CTA #** | 00316/0243/001 |
| **MREC #** | 12/LO/0637 |
| **Study Design** | Parallel group, randomised (1:1), blinded, placebo-controlled multi-centre trial |
| **Type of Patients to be Studied** | Adults (18 years or older) with *S. aureus* (meticillin-susceptible or resistant) grown from at least one blood culture who have received ≤96 hours of active antibiotic therapy for the current infection, and do not have contraindications to the use of rifampicin (including no suspected active tuberculosis) |
| **Setting** | UK NHS Trusts |
| **Interventions to be Compared** | 2 weeks of rifampicin or placebo in addition to standard antibiotic therapy |
| **Study Hypothesis** | Adjunctive rifampicin will enhance killing of *S. aureus* early in the course of antibiotic treatment, sterilise infected foci and blood faster, and thereby reduce the risk of dissemination, metastatic infection and death |
| **Primary Outcome Measures** | Bacteriological failure/death (all-cause) up to 12 weeks from randomisation |
| **Secondary Outcome Measures** | ▪ All-cause mortality up to 14 days from randomisation<br>▪ Death or clinically defined treatment failure or disease recurrence by 12 weeks (clinical failure being assessed by an independent endpoint committee blind to the treatment allocation)<br>▪ Duration of bacteraemia (blood cultures will be taken on days 3 and 7 following randomisation)<br>▪ Adverse events (grade 3/4 adverse events, serious adverse events, adverse events of any grade leading to modification of rifampicin/placebo dose or interruption/early discontinuation)<br>▪ Modification of any treatment (including concomitant medications) due to drug interactions<br>▪ Development of rifampicin resistant *S. aureus*<br>▪ Cost-effectiveness of rifampicin |

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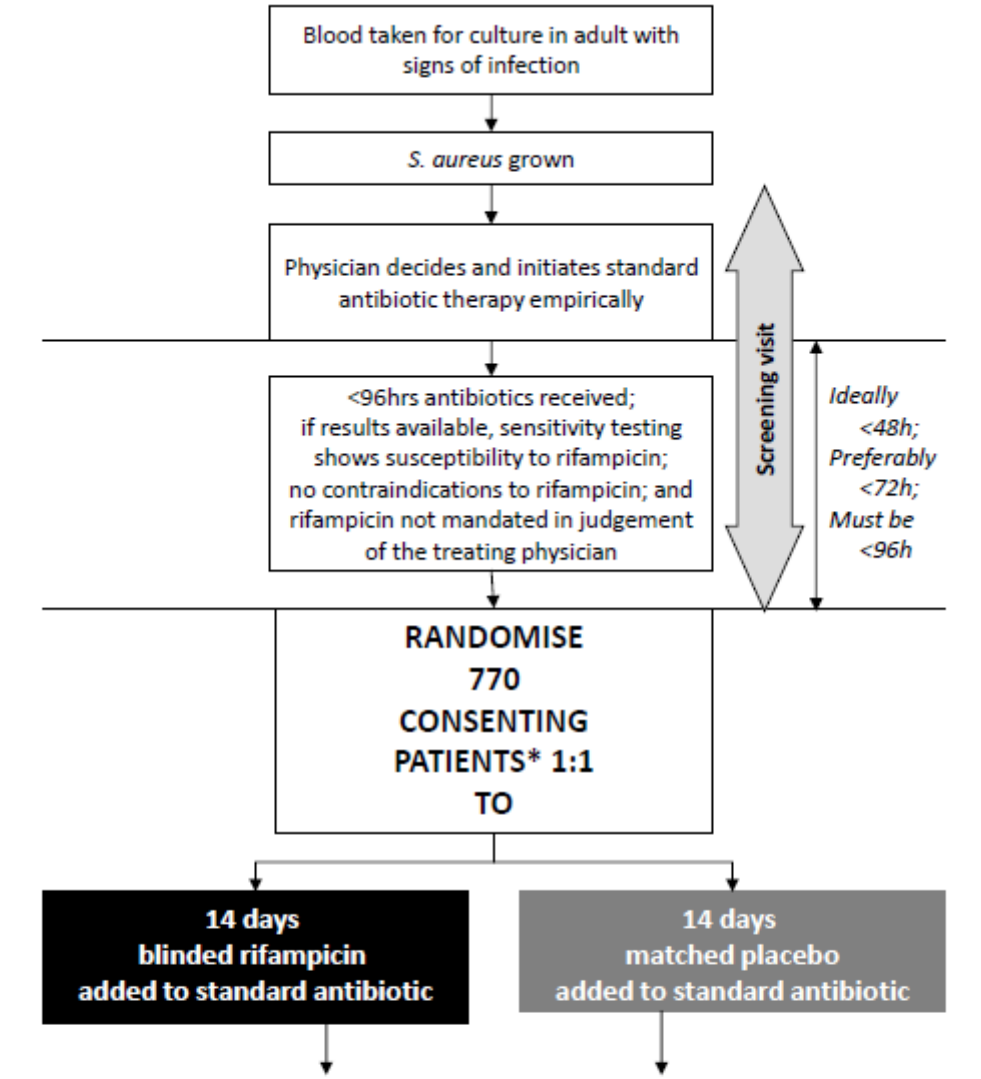
| **Randomisation** | Patients will be allocated 1:1 to rifampicin or blinded placebo using a 24h web service, stratified by site |
| **Number of Patients to be Studied** | 770 |
| **Duration** | ▪ Patients will be recruited over 3.5 years<br>▪ Each intervention will be administered in addition to standard antibiotics for 2 weeks<br>▪ Each patient will be followed for 12 weeks in the trial<br>▪ The overall trial duration is 4.5 years (including start-up and close-out) |
| **Ancillary Studies/Substudies** | 1) A population pharmacokinetic (PK) and pharmacodynamic (PD) study of rifampicin, flucloxacillin and vancomycin for the treatment of *S. aureus* bacteraemia<br>2) The influence of host and bacterial genetics on disease severity and outcome from *S. aureus* bacteraemia<br>3) Experiences of being approached for trial participation, the consenting process and trial participation |
| **Sponsor** | Medical Research Council (MRC) |
| **Funder** | Health Technology Assessment Programme of the National Institutes of Health Research (10/104/25) |
| **Trial Manager** | Janet Cairns |
| **Chief Investigator** | Professor Guy Thwaites |
| **MRC CTU at UCL Project Leader** | Professor A. Sarah Walker |

## TRIAL SCHEMA




*Incapacitated adults would be eligible provided they had an appropriate legal representative.

## TRIAL ASSESSMENT SCHEDULE

| | DAY | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SCR-EEN -ING | 0 | 1 | 2 | 3 | 5 | 7 * | 10 * | 14 * | WEEKLY UNTIL DISCHARGE | 84 | POTENTIAL FAILURE /RECURRENCE |
| **ALL PATIENTS** | | | | | | | | | | | | |
| Eligibility assessment | X | | | | | | | | | | | |
| Patient information sheet and consent | X | | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | | |
| Clinical assessment [a] | | X | | | X | | X | X | X | X | X | X |
| Resource utilisation [b] | | X | | | | | X | | X | X | X | |
| EQ-5D | | X | | | | | X | | X | | X | X |
| Blood culture with sensitivities (10ml)[c] | (X) | X | | | X | | X | | | | | X |
| EDTA blood [d] (1.5ml) | | X | | | | | | | | | | |
| Clotted blood [e] (5 ml) | | | | | | | | | | | | |
| CRP | (X) | X | | | X | | | X | X | | | X |
| ALT, ALP, bilirubin | (X) | | | | X | | | X | | | | |
| Serum Storage | | X | | | X | | | | X | | | |
| Whole blood [f] (5ml) | | X | | | | | | | | | | |
| Nasal bacterial swab [g] | | X | | | | | | | | | | |
| **SUBSET OF PATIENTS RECRUITED TO THE INTENSIVE PK/PD substudy [h]** | | | | | | | | | | | | |
| Lithium heparin blood (8x3ml in total) for antibiotic concentration assays [i] | | | X | | X | | X | | | | | |
| Lithium heparin blood (10ml) for compartment studies [j] | | X | X | X | X | X | X | X | X | | | |
| Clotted blood [e] (5ml) | | | | | | | | | | | | |
| CRP | | X | X | X | X | X | X | X | X | | | X |
| ALT, ALP, bilirubin | | | | | X | | | X | | | | |
| creatinine | | X | | | X | | | X | | | | |
| serum storage | | X | X | X | X | X | X | X | X | | | X |
| Blood culture (10ml) | | X | X | X | X | X | X | X | X | | | X |
| **SUBSET OF PATIENTS RECRUITED TO THE SPARSE PK/PD substudy [k]** | | | | | | | | | | | | |
| Lithium heparin blood (3x3ml in total) for antibiotic concentration assays[k] | | | X | | X | | | | | | | |
| Clotted blood [e] (5ml) | | | | | | | | | | | | |
| CRP | | X | | | X | | | X | X | | | X |
| ALT, ALP, bilirubin | | | | | X | | | X | | | | |
| creatinine | | X | | | | | | | | | | |
| serum storage | | X | | | X | | | | X | | | X |
| Blood culture (10ml) | | X | X | X | X | | X | | | | | X |

*() indicate tests that will have already been performed as part of standard management.*

* If a patient has already been discharged from hospital before day 7, 10, or 14, additional investigations requiring a blood draw (culture, CRP, ALT, ALP, bilirubin, serum storage) are not required so patients should not be asked to attend ARREST specific outpatient appointments on these days, but to return at 12 weeks only. If however a patient is attending outpatient appointments for other reasons then please collect blood samples for these visits if possible.

(a) Including likely source and focus of infection, co-morbidities, duration of symptoms, temperature, record of concomitant medications (including all non-study antibiotics) at enrolment. Follow-up assessments will record new symptoms and signs indicating secondary site infections, all surgical interventions performed to treat the disease, grade 3 or 4 or serious adverse events, adverse events of any grade leading to modification of rifampicin/placebo dose or interruption/early discontinuation, any drug interactions leading to dose modification of any drug (including concomitant medications), and all changes in antimicrobial prescribing.

(b) Resources used whilst in hospital will be recorded by health care professionals (or any assigned representatives). These will include days spent in wards, procedures or laboratory tests undertaken and concomitant medication. After discharge, resource use will be self-reported by the patient. A data collection form will be developed that records post-discharge re-hospitalisations and contact with clinicians (hospital, GP, etc).

(c) Blood cultures will have already been taken prior to the screening assessment from which the potential *S. aureus* bacteraemia will have been identified. *S. aureus* isolated from blood cultures taken on days 0, 3 and 7 must have at least rifampicin susceptibility tests performed in order to evaluate the secondary endpoint acquisition of rifampicin resistance, although typically the routine panel of antimicrobial sensitivities will be performed (all susceptibilities will be recorded). All *S. aureus* isolates to be stored locally, then shipped annually to central storage facility in Oxford and Brighton for biobanking. All repeat isolates will be genotyped to define relapse or re-infection. **Blood cultures may be taken at any other timepoints necessary for clinical management of the patient.** If these are considered to reflect potential failure of treatment or recurrence, then sensitivities should be performed as above. Results of any additional blood cultures done should be recorded on ARREST CRFs, and *S. aureus* isolates stored and rifampicin susceptibility tested.

(d) For measurement of Haemoglobin, white cell count, lymphocytes, neutrophils, platelets

(e) For measurement of C-reactive protein (CRP); alanine transaminase (ALT), bilirubin and alkaline phosphatase (ALP) at timepoints shown. Serum creatinine will only be measured in the PK/PD substudies on days 0, 3, and 10. 2ml of serum will be saved from clotted blood taken as shown, stored locally, then shipped to a central archive at King's College London. CRP and liver function tests are routine investigations for patients with suspected *S. aureus* bacteraemia, and results of pre-screening investigations should also be recorded on the screening CRF.

(f) 2.5 mls into EDTA and 2.5 mls into PAXgene blood RNA tube (Qiagen). Store EDTA blood for later DNA extraction and PAXgene tube for later RNA extraction. Samples will be stored locally before shipping to King's College London for DNA/RNA extraction and archiving if the patient has consented for human DNA/RNA storage.

(g) A single nasal swab for *S. aureus* culture will be taken at baseline. The anterior nasal swab should be stored at $4^0$C before sending, within 2 working days, to Brighton and Sussex University Hospital (Dr Martin Llewelyn) where it will be cultured and the bacteria archived. Refer to the ARREST Laboratory Manual for more details.

(h) Only patients enrolled at Guy's and St. Thomas', Addenbrookes, and University College London Hospitals will be approached. See Section 11.2 p58 for more details and the PK/PD laboratory manual.

(i) A total of 8x3ml blood samples will be taken for drug concentration assays. Aliquots of plasma will be rapidly frozen at -$70^0$C and stored locally before shipment in batches to University of Liverpool (Dr Gerry Davies) for subsequent measurement of antibiotic concentrations. Samples will be taken at specified time points following the study drug being given on day 1, 3 and 7. See Section 11.2 p58 for more details and the PK/PD laboratory manual.

(j) Please note: the collection and processing of whole blood for component studies is site specific and will only occur when local resources and personnel allow. Please consult the local PI. 10ml of blood will be taken and centrifuged over fycol to separate the blood into plasma, peripheral blood mononuclear cells, and neutrophil fractions. Each fraction will be cultured and cells will be frozen for later characterisation.

(k) A total of 3x3ml blood samples will be taken for drug concentration assays. Only patients enrolled at Oxford, Liverpool, and Brighton will be approached. Samples will be taken at specified time points following the study drug being given on day 1 and 3 depending on whether patients follow the sparse A or sparse B sampling schedule. See Section 11.2 p58 for more details and PK/PD laboratory manual.

## CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine transaminase |
| ALP | Alkaline phosphatase |
| AR | Adverse reaction |
| AUC | Area under the curve |
| CART | Classification and Regression Tree |
| CEAC | Cost effectiveness acceptability curve |
| CI | Chief Investigator |
| CI | Confidence interval |
| CLRN | Comprehensive Local Research Network |
| CRF | Case Report Form |
| CRP | C-reactive protein |
| CTA | Clinical Trials Authorisation |
| CTC | Common Toxicity Criteria |
| CTIMP | Clinical trial of an investigational medicinal product |
| CTU | Clinical Trials Unit |
| CV | Coefficient of Variation |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| DPA | (UK) Data Protection Act |
| ERC | Endpoint Review Committee |
| EudraCT | European Union Drug Regulatory Agency Clinical Trial |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HAI | Healthcare Associated Infection |
| HPA | Health Protection Agency |
| HTA | Health Technology Assessment |
| ICER | incremental cost effectiveness ratio |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IMP | Investigational medicinal product |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| ITT | Intention-to-treat |
| IV | Intravenous |
| KCL | King's College London |
| KHP CTO | King's Health Partners Clinical Trials Office |
| LR | Legal representative |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRC | Medical Research Council |
| MRC CTU at UCL | Medical Research Council Clinical Trials Unit at University College London |
| MREC | Main Research Ethics Committee |
| MRSA | Meticillin-resistant *Staphylococcus aureus* |
| MSSA | Meticillin-sensitive *Staphylococcus aureus* |
| NHS | National Health Service |
| NICE | National Institute for Health and Clinical Excellence |
| NIHR | National Institute for Health Research |
| NNT | Number needed to treat |
| PEG | Percutaneous Endoscopic Gastrostomy |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| PD | Pharmacodynamic |
| PK | Pharmacokinetics |
| QALY | Quality adjusted life year |
| QMC | Quality Management Committee |
| QoL | Quality of life |
| R&D | Research and Development |
| REC | Research Ethics Committee |
| RGF | Research Governance Framework (for Health and Social Care) |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAR | Serious adverse reaction |
| SOP | Standard operating procedure |
| SPC | Summary of Product Characteristics |
| SSI | Site-specific information |
| SURF | Service Users Research Forum |
| SUSAR | Suspected unexpected serious adverse reaction |
| TOE | Transoesophageal echocardiography |
| TM | Trial Manager |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TMT | Trial Management Team |
| TSC | Trial Steering Committee |
| UAR | Unexpected adverse reaction |
| UCL | University College London |
| ULN | Upper limit of normal |

| | |
|---|---|
| UKCIRG | United Kingdom Clinical Infection Research Group |

# 1 BACKGROUND

## 1.1 THE MANAGEMENT OF *S. AUREUS* BACTERAEMIA

We have recently reviewed the evidence to guide the optimal management of *S. aureus* bacteraemia and found that fewer than 1500 patients have been entered in 16 randomised controlled trials (RCT) of *S. aureus* bacteraemia antimicrobial therapy published over the last 50 years (1). Despite scant data from controlled trials, current treatment guidelines recommend that *S. aureus* bacteraemia should be treated with at least 14 days of an intravenous (IV) beta-lactam antibiotic, or a glycopeptide if the bacteria are meticillin-resistant. Combination antimicrobial therapy is generally not recommended, except in severe meticillin-resistant *S. aureus* (MRSA) infections (e.g. endocarditis, prosthetic joint infections) (2-5). Most of the recommendations are based on uncontrolled observational studies and clinical experience, and views of how to manage *S. aureus* bacteraemia differ widely (6-7).

To estimate the degree of uncertainty around clinical practice within the NHS we conducted a multi-centre, prospective observational study of patients with *S. aureus* bacteraemia. The findings from the first year (November 2008-2009; 549 cases) revealed that management varied widely among NHS Trusts, with little adherence to the published guidelines (8). Centres varied significantly ($p<0.01$) in the proportions given oral treatment alone for >50% of treatment (range 12-40% across NHS Trusts), in those treated for longer than 28 days (range 13-54%), and in those given combination antimicrobial therapy (range 14-94%). Twenty four percent of patients died during admission, 72% within the first 14 days of treatment. Older age, longer time in hospital before bacteraemia, and an unidentified infection focus were independent predictors of in-hospital death ($p<0.001$).

Our literature review and observational study confirm *S. aureus* to be a common, frequently fatal blood infection within NHS Hospitals - yet the optimal management remains uncertain and practice highly variable. In particular, key questions concerning the most effective antimicrobial regimen are unanswered, and will remain so until they have been addressed by large, well-conducted RCT. For reasons described below, one major clinical research priority is to assess the role of adjuvant antibiotic therapy.

## 1.2 HOW MIGHT ADJUNCTIVE RIFAMPICIN IMPROVE OUTCOME FROM *S. AUREUS* BACTERAEMIA?

Three properties make rifampicin an attractive, if unproven, antibiotic for *S. aureus* bacteraemia treatment. First, it has good oral bioavailability (9). Second, it penetrates cells, tissues, and biofilms better than beta-lactam and glycopeptide antibiotics (the current mainstays of *S. aureus* bacteraemia treatment) and, therefore, in combination with these agents, may resolve serious *S. aureus* infections faster and more effectively (10). And third, it is cheap: a daily 600mg dose costs £0.73 by mouth and £7.67 intravenously (11).

The best clinical predictor of complications and death from *S. aureus* bacteraemia is the persistence of bacteria in blood 48-96 hours after the start of active antimicrobial therapy (12-14). Persistent bacteraemia (>48 hours) occurs in around 40% of patients, despite prompt removal of any infected focus and effective antimicrobial therapy (12-13), and increases the patient's risk of metastatic complications and death nearly five-fold (12). Why *S. aureus* persists in blood despite treatment with antibiotics with good *in vitro* activity is uncertain, but is probably explained by the failure of currently recommended first-line antibiotics (beta-lactams and glycopeptides) to kill bacteria associated with either pus (dead or dying neutrophils), viable cells, or biofilms. The well-documented

survival of *S. aureus* within each of these ecological niches may lead to persistent bacterial seeding of the bloodstream and recurrent, recalcitrant infection. In addition, we have recently proposed that bloodstream neutrophils may act as "Trojan horses" for *S. aureus* dissemination, providing bacteria with further protection from first-line antibiotics with poor intracellular activity such as the recommended beta-lactams and glycopeptides (15).

Rifampicin, clindamycin, the tetracyclines and the fluoroquinolones are all concentrated within cells but, with the exception of rifampicin, their activity is reduced in the acidic environments found within intracellular phagolysosomes (16-17). Rifampicin has repeatedly been shown to be highly effective against *S. aureus* within cells (17-18) and against bacteria associated with biofilms and prostheses (10, 19). Beta-lactams and glycopeptides do not pass easily into eukaryotic cells or biofilms, and kill *S. aureus* associated with these niches less effectively than free, extracellular bacteria (20-21). Data from animal models of severe *S. aureus* infections have generally shown rifampicin-containing antibiotic combinations to be superior with respect to reduced bacteria counts, sterilisation and cure rates, independent of the model used (10). Yet, despite the breadth of these experimental findings, the potential advantages of adjunctive rifampicin for the treatment of severe *S. aureus* infections in humans remain theoretical. There are insufficient data from only 246 patients randomised between rifampicin vs non-rifampicin containing regimens in controlled trials to confirm or refute a beneficial effect.

### 1.3 WHAT ARE THE POTENTIAL PROBLEMS OF USING ADJUNCTIVE RIFAMPICIN FOR S. AUREUS BACTERAEMIA?

There are three important potential problems with using rifampicin for the treatment of *S. aureus* bacteraemia: the development of rifampicin resistant bacteria, interactions with other drugs, and hepatic toxicity. Resistance can be acquired rapidly when rifampicin is used alone in treatment, resulting from mutations in the drug's binding site (the β-subunit of the bacterial DNA-dependent RNA polymerase). Interactions with other drugs are mediated by rifampicin's ability to increase their metabolism through the potent induction of the hepatic cytochrome p450 system. Lastly, rifampicin can cause hepatic toxicity, although the enormous worldwide experience of using rifampicin for the prevention and 6-month treatment of tuberculosis confirms the drug is extremely well-tolerated and causes clinically significant hepatitis in <1% of patients (22).

The frequency with which rifampicin resistance develops during the combination therapy of *S. aureus* bacteraemia and the factors associated with its development are difficult to assess from the published literature. New resistance was not reported in any of the 433 patients treated with adjunctive rifampicin in three recent, but non-randomised, clinical studies of *S. aureus* bacteraemia and other serious *S. aureus* infections (23-25), giving an observed incidence of 0% with upper 97.5% confidence limit of 0.8%. However, other clinical series have reported the emergence of rifampicin resistance in 20-40% of patients after a median 9-12 days of treatment (range 5-58 days) (26-28). One of these studies, a retrospective description of 42 rifampicin-treated patients with native valve *S. aureus* endocarditis, reported those who developed resistance (21%) were more likely to have prolonged bacteraemia than a selected control group not given rifampicin, although the controls had significantly less severe disease at the start of treatment (26). The investigators also reported that rifampicin had clinically important interactions with other drugs in 52% of patients, but a high proportion of patients were co-infected with HIV (18%) and/or hepatitis C (48%), and required methadone (which interacts with rifampicin) for opiate addiction (57%). This population were also at high risk for rifampicin-related hepatic toxicity, but hepatic dysfunction occurred in only 9 patients; all were infected with hepatitis C and had abnormal liver function tests before starting rifampicin.
In summary, there are insufficient clinical data to determine the true incidence of rifampicin resistance, drug interactions, and hepatic toxicity. Only a large, randomised controlled trial will

provide these data and allow the potential risks of adjunctive rifampicin to be properly balanced against the potential benefits.

## 1.4 ADJUNCTIVE RIFAMPICIN FOR *S. AUREUS* BACTERAEMIA: CURRENT CLINICAL EVIDENCE, GUIDELINES, AND PRACTICE

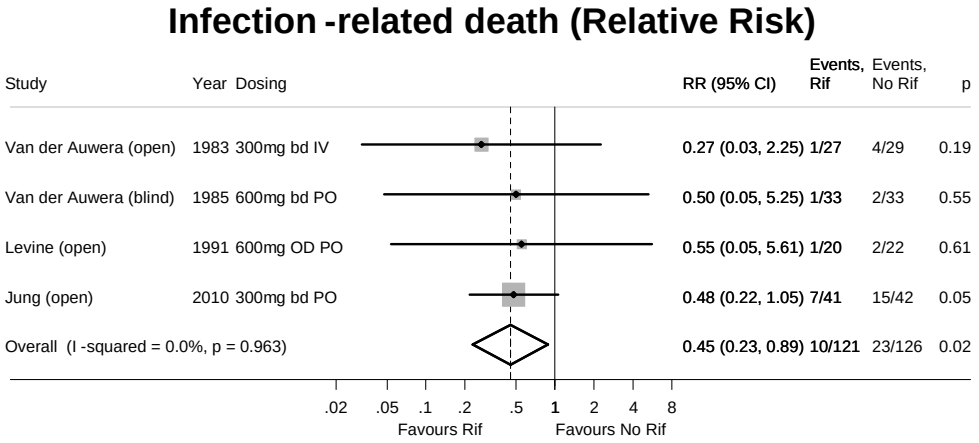
Four randomised controlled trials, involving 246 patients in total, have examined the effectiveness of adjunctive rifampicin for serious *S. aureus* infections, including patients with bacteraemia (29-32). The first two trials, published more than 25 years ago, enrolled adults with any serious *S. aureus* infection, of whom 47/121 (39%) were bacteraemic at randomisation (29, 33). The third trial enrolled 42 adults, all with *S. aureus* bacteraemia and endocarditis (31), and the fourth enrolled 83 adults admitted to an intensive care with MRSA pneumonia; only 9/83 (11%) were bacteraemic (32). We performed a stratified meta-analysis of the results from these trials (figure 1, p18); sub-group analysis of bacteraemic adults was possible for all but the fourth trial, which did not provide sufficient data. Overall, adjunctive rifampicin reduced infection-related deaths by 55% (p=0.02) and bacteriological failure by 58% (p=0.004), with similar (54%, 77%) but non-significant (p=0.22, p=0.17) reductions in the bacteraemic subgroup (n=89).

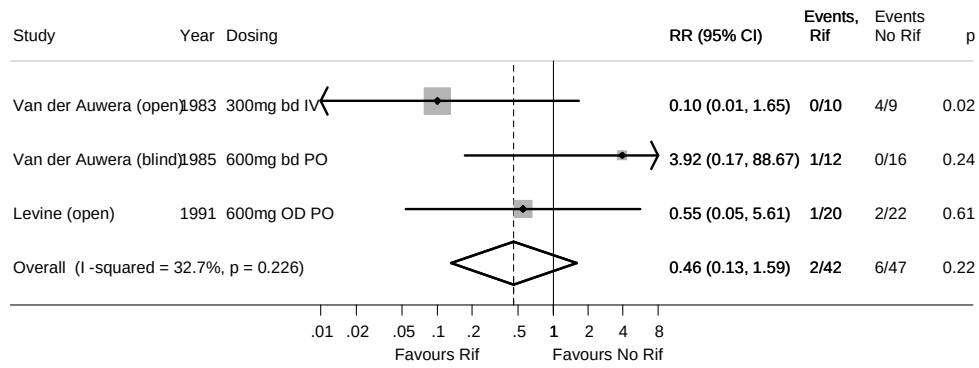
The daily dose of rifampicin in these studies varied from 600mg to 1200mg. Significant drug interactions were not reported in any of the studies, and details concerning hepatic toxicity were not provided in the first 3 trials. The most recent trial reported 6/41 (15%) patients treated with rifampicin developed hyperbilirubinaemia (compared to 1 control patient) but the impact on treatment was not described. This trial was also the only one to report rifampicin resistance developing on treatment: new resistance was found in 14/41 (34%) rifampicin-treated patients, although it did not appear to have a significant impact on clinical cure rates (32).

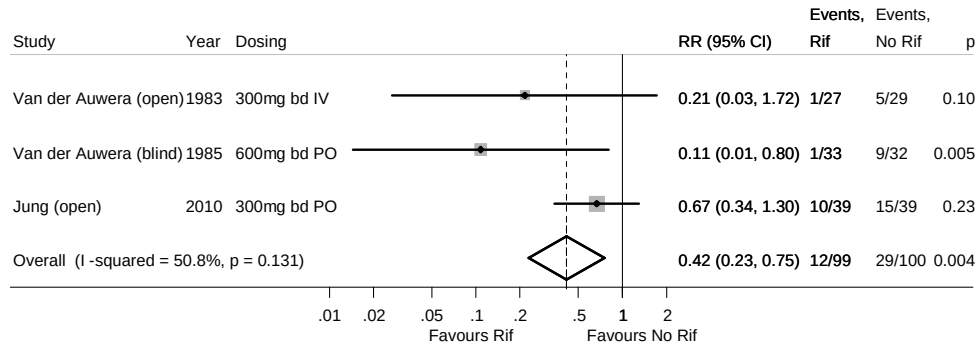
There are limited data from uncontrolled, observational studies supporting the use of adjunctive rifampicin, although, given the potential for confounding by indication, their results must be interpreted cautiously. A prospective study of 381 adults with *S. aureus* bacteraemia found the mortality of those with severe disease was halved in those who received adjunctive rifampicin (mortality 38% vs 17%, p<0.001), without an increased incidence of rifampicin resistance (24). A recent retrospective analysis of patients with staphylococcal sternal wound infections, 35% of whom had *S. aureus* bacteraemia, reported adjunctive rifampicin was independently associated with a reduced risk of treatment failure (hazard ratio 0.26, 95% CI 0.10–0.64, P=0.004) (25).

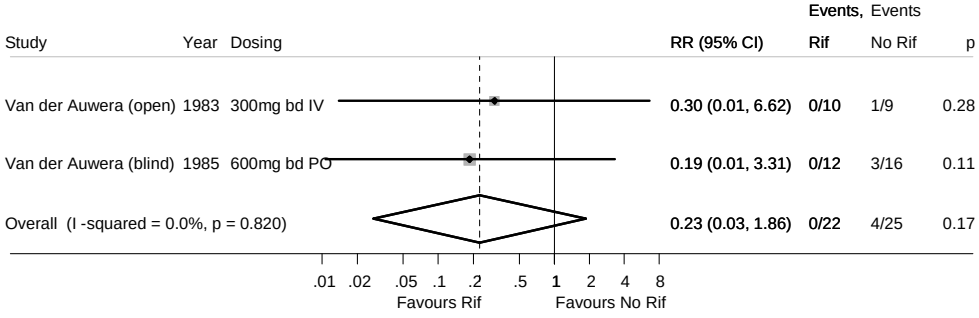
Our own observational study found 17% of NHS patients with *S. aureus* bacteraemia were treated with rifampicin, but with large variations in use across the 6 centres (range 1-75% of patients) (8). Rifampicin was used to treat 21% of MRSA bacteraemia and 15% of meticillin-susceptible bacteraemia and was not reserved for severe, complex disease as the guidelines suggest: 13% of uncomplicated IV catheter-related bacteraemia were treated with rifampicin. However, rifampicin was given more often to patients with MRSA bacteraemia resulting from foci other than IV catheters – although even in this indication only 24% received it. An unadjusted comparison of in-patient mortality showed 23% of patients not treated with rifampicin died compared with 13% given rifampicin (P=0.03). The impact on survival appeared to be more marked in those with a non-removable focus of infection (whose in-patient mortality was higher), although there was no statistical evidence supporting smaller relative effects of adjunctive rifampicin in those with removable foci (p=0.39).

**Figure 1. Meta-analysis (fixed effects) of 4 trials of adjunctive rifampicin for severe S. aureus disease, including bacteraemia.**



The results of the meta-analysis together with data from observational studies indicate adjunctive rifampicin may have a surprising and substantial impact on survival from *S. aureus* bacteraemia. They do not, however, constitute evidence of sufficient rigor to influence current treatment guidelines, clinical practice, or indeed the equipoise of clinicians recruiting patients into the proposed trial – even clinicians in centres using rifampicin in a greater proportion of patients have indicated their willingness to randomise as they recognise the lack of evidence supporting their practice. In particular, whilst statistically significant, the results from the trial meta-analysis are not convincing as they are based on a small number of patients in a small number of trials over a wide period of time. In addition, the potential negative impacts of rifampicin toxicity, interactions and resistance cannot reliably be assessed in these studies. Current USA and UK guidelines only recommend adjunctive rifampicin for the treatment of severe MRSA infections, specifically endocarditis, bone and joint infections, and infections involving prostheses (category II evidence) (3, 5). But with weak support for these recommendations it is unsurprising few physicians follow them in practice.

Finally, the UKCIRG has continued to collect prospective data on patients with *S. aureus* bacteraemia, expanding to involve 15 NHS centres. As of July 2011, UKCIRG has data on more than 1600 patients; 20% received rifampicin. Physicians at these centres will be responsible for recruiting patients to the proposed trial, although other centres may also join. UKCIRG centres have confirmed they consider that sufficient equipoise regarding the value of adjunctive rifampicin exists at a population level to randomise the majority of cases.

## 1.5 HYPOTHESIS AND OBJECTIVES

The hypothesis is that adjunctive rifampicin will enhance killing of *S. aureus* early in the course of antibiotic treatment, sterilise infected foci and blood faster, and thereby reduce the risk of dissemination, metastatic infection and death.

Therefore, the primary objective of the trial is to investigate the impact of adjunctive rifampicin on bacteriological failure or death through 12 weeks from randomisation.

Secondary objectives include:

- evaluating the impact of rifampicin on all cause mortality up to 14 days from randomisation
- assessing toxicity and emergence of resistance associated with adjunctive rifampicin
- identifying the duration of bacteraemia and potential mechanisms of action of rifampicin through PK/PD investigations
- assessing the cost effectiveness of the use of adjunctive rifampicin and other antibiotic therapy for *S. aureus* bacteraemia in the NHS.

# 2 SELECTION OF SITES/CLINICIANS

The Medical Research Council as trial sponsor has overall responsibility for site and investigator selection.

## 2.1 SITE/INVESTIGATOR SELECTION CRITERIA

To participate in the ARREST trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the ARREST Trial Management Group (TMG) and are defined below.

### 2.1.1 SITE PRINCIPAL INVESTIGATOR QUALIFICATIONS & AGREEMENTS

The investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, and/or the regulatory authority(ies).

The investigators should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current SPC and in any other information sources provided by the Sponsor.

The investigators should be aware of, and should comply with, the principles of ICH GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

The investigators/sites should permit monitoring and auditing by the Sponsor(s), and inspection by the appropriate regulatory authority

The investigators should maintain a delegation log of appropriately-qualified persons to whom the investigator from each site has delegated significant trial-related duties.

The investigators should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

### 2.1.2 ADEQUATE RESOURCES

- The investigators should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (that is, the investigator regularly treats the target population).

- The investigators should have an existing *S. aureus* bacteraemia ward consultation service which takes an active part in the management of all hospitalised patients with *S. aureus* bacteraemia.

The investigators should have sufficient time to properly conduct and complete the trial within the agreed trial period.

The investigators should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigators should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

The sites should have sufficient data management resources to allow prompt data return to the MRC CTU at UCL. Sites that have previously participated in MRC CTU at UCL-coordinated trials in the same disease area should have a proven track record of good data return.

### 2.1.3 SITE ASSESSMENT

Once a site has been identified as being compliant with these selection criteria, the trial team will provide the site with a copy of this protocol, a trial summary and the Summary of Product Characteristics (SPC) for rifampicin, and other ARREST master file documentation to submit for their local R&D approval.

Sites where a previous serious protocol breach has occurred will be visited and thoroughly reviewed before allowing patients to enter the trial.

Each selected clinical trial site must complete the ARREST Accreditation Form at the same time as applying for their local R&D approval, which includes the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the site. In addition and in compliance with the principles of ICH GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the MRC CTU at UCL. The MRC CTU at UCL must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File (TMF) at the site and also at the MRC CTU at UCL. A clinical trial agreement will also be signed by the NHS Trust or Board (see Section 14 - Finance p67). Local laboratory normal ranges must also be provided.

## 2.2 APPROVAL AND ACTIVATION

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating site principal investigators. Trial staff at the MRC CTU at UCL will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering patients.

On receipt of the above documents at the MRC CTU at UCL, together with the local R&D approval and the clinical trial agreement with the local NHS Trust, written confirmation will be sent to the PI. Trial specific training will be performed for trial site staff. A laboratory supplies pack will be provided to the site. The site's pharmacist will also be informed of the site's activation and an initial drug order will be dispatched to the named pharmacist in the Pharmacy Plan document.

The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority,and the REC.

The PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the MRC CTU at UCL using a protocol deviation form.

A list of activated sites may be obtained from the Trial Manager.

# 3 SELECTION OF PATIENTS

There will be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed locally prior to attempting to randomise the patient – clarifications may be sought from the ARREST Trial Manager or Chief Investigator.

The eligibility criteria for this trial have been carefully considered. The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that **no exceptions** be made to these criteria for admission to the study.

Patients will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below. Of note, *S. aureus* bacteraemia is a serious infection whose standard treatment requires IV antibiotics. Therefore all eligible patients will already be hospital inpatients.

## 3.1 PATIENT INCLUSION CRITERIA

- Adults (18 years or older)
- *Staphylococcus aureus* (meticillin-susceptible or resistant) grown from at least one blood culture
- Less than 96 hours of active antibiotic therapy for the current infection, not including rifampicin, and excluding any stat doses.
- Patient or legal representative (LR) provides written informed consent

The formal inclusion criteria is having received <96 hours of active antibiotic therapy for the current infection. However, the best clinical predictor of complications and death from *S. aureus* bacteraemia is the persistence of bacteria in blood 48-96 hours after the start of active antimicrobial therapy (12-14), and therefore, if the study hypothesis is correct, rifampicin would have maximal impact when initiated as soon as possible. Therefore, patients should be included in the trial as soon after initiation of active antibiotic therapy as possible, within 48 hours wherever possible and ideally within 72 hours. Planned subgroup analysis will investigate heterogeneity in any treatment effect according to time from active antibiotic therapy (see Section 9.5 - Analysis Plan (Brief) p53).

Following the Medicines for Human Use (Clinical Trials) Regulations 2004, the legal representative (LR) is:

- A person independent of the trial, who by virtue of their relationship with the potential study participant (e.g. a relative or person providing care) is suitable to act as their representative for the purposes of the trial, and who is available and willing to so act for those purposes.

*Or if there is no such person:*

- A person independent of the trial, who is the doctor primarily responsible for the medical treatment provided to that adult.
- Or a person nominated by the relevant healthcare provider.

The written informed consent provided by legal representative should reflect the presumed will of the patient.

## 3.2 PATIENT EXCLUSION CRITERIA

- Infection not caused by *S. aureus* alone in the opinion of the infection specialist (e.g. *S. aureus* is considered a blood culture contaminant, or polymicrobial culture with another organism likely to be contributing clinically to the current infection)
- Sensitivity results already available and demonstrate rifampicin resistant *S. aureus* (defined by British Society for Antimicrobial Chemotherapy *in vitro* disc susceptibility testing or by Vitek testing)
- Infection specialist, in consultation with the treating physician, considers rifampicin is contraindicated for any reason
- Infection specialist, in consultation with the treating physician, considers rifampicin treatment is mandatory for any reason
- Infection specialist suspects active infection with *Mycobacterium tuberculosis*
- Previously been randomised in ARREST for a prior episode of *S. aureus* bacteraemia

As the underlying hypothesis is that rifampicin may improve outcomes by increasing the rate of early bacterial killing, results of *in vitro* sensitivity testing are not required before randomisation, as it will be important to initiate rifampicin as soon as *S. aureus* is identified. This will also ensure that results are generalisable to empiric treatment of *S. aureus* bacteraemia in the future. However, if for any reason *in vitro* susceptibility results are already available at the point where randomisation would be considered, and demonstrate rifampicin resistance, then the patient will not be eligible.

Patients who are randomised when results of *in vitro* susceptibility testing are not yet available and are subsequently found to have rifampicin-resistant *S. aureus* will discontinue blinded trial treatment (without unblinding) and continue follow-up through 12 weeks (see Section 5.6 - Protocol Treatment Discontinuation p34). Secondary efficacy analyses will be conducted excluding these patients (see Section 9.5 - Analysis Plan (Brief) p53). Based on the existing observational study, such patients are expected to contribute ~1% of the total enrolled.

## 3.3 NUMBER OF PATIENTS

770 patients (385 in each treatment arm) will be enrolled over a target of 3.5 years.

## 3.4 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

Patients will be identified through the clinical microbiology laboratory and the infectious diseases/microbiology consult service of each centre. All the trial centres run a clinical consult service for all cases of *S. aureus* bacteraemia and identify such patients as soon as their blood cultures become positive. The infectious diseases physicians and microbiologists responsible for this service will alert their colleagues responsible for trial recruitment and they will arrange for the patient to be seen and assessed for eligibility. When possible, patients will be screened for eligibility on the day their blood cultures flags positive with *S. aureus*; this usually takes 24-48 hours from innoculation of the culture bottle.

The name, date of birth and hospital number of every adult screened for ARREST should be added to the site Screening & Randomisation Register, together with allocated trial number if subsequently randomised, or the reason the patient was not randomised. The Screening & Randomisation Register should be kept in a secure location at each site and will be the responsibility of the site Principal Investigator.

Written informed consent to enter into the trial and be randomised must be obtained from patients or a person with responsibility (including legal authorities) (a legal representative, LR). This should be, if appropriate, after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the trial, including for the screening assessment (see Appendix II - Template Patient information sheets p81 and Appendix III - Trial Consent forms p89).

It must be made completely and unambiguously clear that the patient (or legal representative) is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment. If consent was provided by a legal representative, the patient should be consulted and consent recorded if and when they have the capacity to do so.

Signed consent forms must be kept by the investigator and documented in the CRF and a copy given to the patient or family. Consent to inform the patient's General Practitioner (GP) of the trial and the patient's involvement in it will be included (see Appendix III - Trial Consent forms p89 and Appendix IV - GP letter p93).

After consent has been obtained from the patient or their legal representative, clinical information including medical history and examination, and weight will be recorded on the screening Case Record Form (CRF) (see Trial Assessment Schedule page viii). CRP and liver function tests are routine investigations for patients with suspected *S. aureus* bacteraemia, and results of these routine tests will also be recorded on the screening CRF as part of the medical history of the current infection.

The screening visit will take place as soon as possible after a potential patient has been identified by the Microbiology laboratory. The trial's central hypothesis is that ***early*** intervention with rifampicin enhances bacterial killing and improves clinical outcome. Therefore, it is essential patients are randomised as early as possible in their treatment and by the limit defined by the inclusion criteria of <96 hours of active antibiotic therapy for the current infection. For this reason trial teams should request patient's consent to recruitment within 2 hours of the screening assessment wherever possible, and ideally within 4 hours.

### 3.4.1 INCLUSION OF INCAPACITATED ADULTS

Incapacitated adults with *S. aureus* bacteraemia will be eligible to enter the trial. These adults will tend to have more severe infection (e.g. because the infection is severe enough for admission to an intensive care unit) and therefore stand most to gain from the enhanced anti-microbial activity of rifampicin. Such patients can be included in the trial providing a legal representative (LR) gave written informed consent. We anticipate around 10% of patients with *S. aureus* bacteraemia lack capacity; the majority of these will be critically ill and incapacitated on intensive care. In these circumstances, the site PI, or another experienced and independent physician will follow the Mental Capacity Act (2005) to formally assess the capacity of the individual to make an informed decision to participate in the trial. If incapacity is confirmed, written informed consent would be sought from either a personal (e.g. a relative) or a nominated LR (e.g. Consultant Intensivist caring for the patient, but not involved in the trial). If the subject regains capacity during treatment they will be informed of the consent given by their LR and their wishes respected concerning on-going participation. If they are happy to remain in the trial, the patient should complete a patient consent form at this time (Appendix III - Trial Consent forms p89). If they wish to withdraw from the trial, no further trial-related procedures will be performed, but data to this point would be used in analysis. Data from any patient who dies before regaining capacity (but whose LR has provided consent) will be included in analysis.

# 4 RANDOMISATION

Eligibility will be confirmed via the Screening CRF on the ARREST database and patients randomised to two parallel groups in a 1:1 ratio: standard intravenous antibiotic therapy plus 14 days placebo, or standard intravenous antibiotic therapy plus 14 days rifampicin. Randomisation will be stratified by clinical site, as blinded drug (in fully made-up and labelled treatment packs) will be pre-shipped to local pharmacies. Randomisation lists will be computer-generated based on random permuted blocks. A 24h web-based randomisation service will be provided via the ARREST database.

## 4.1 RANDOMISATION PRACTICALITIES

Before randomisation, the patient's eligibility should be confirmed by completing the first section on the Screening CRF. The study doctor should also state whether they plan to initially use IV study treatment or oral study treatment.

The study doctor or nurse should then access the password protected ARREST database for randomisation, using the URL below, and will receive a trial number for the patient which will correspond to a labelled treatment pack which will then be dispensed by the pharmacy. **Treatment should start as soon as possible after randomisation.** The trial number should be added to the Screening & Randomisation Register, together with the date of randomisation. Further details on the process of randomisation can be found in Section 9.1 - Method of Randomisation p51.

**RANDOMISATIONS**
To randomise, please go to https://macro.ctu.mrc.ac.uk/macro/
24h a day, 7 days a week.
If the ARREST database is not available, please complete the Emergency Paper CRF
and fax to **020 7670 4817** or email to **mrcctu.arrest@ucl.ac.uk**

A manual randomisation process has been set up to cover any instances when the database is not working. If the ARREST database is not available, please complete the Emergency Paper Screening CRF and fax to 020 7670 4817 or email to mrcctu.arrest@ucl.ac.uk.

The Enrolment CRF should then be completed (including clinical assessment and resource utilisation since blood was first drawn for culture) and blood drawn for investigations (as summarised in the Trial Assessment Schedule page viii). Completing the Enrolment CRF **after** randomisation enables the blinded drug to be dispensed by the pharmacy whilst the Enrolment CRF is being completed, to ensure patients start trial medication as quickly as possible. Blood samples will be taken for culture, full blood count and C-reactive protein, and whole blood (for DNA/RNA extraction) and serum will be saved.

## 4.2 RANDOMISATION CODES & UNBLINDING

Randomisation codes and unblinding are considered in Section 5.5 - Unblinding p34.

## 4.3 CO-ENROLMENT GUIDELINES

Patients enrolled in ARREST will be acutely sick with *S. aureus* bacteraemia. If patients are already participating in an ongoing randomised trial or observational study (e.g. of cardiovascular

prevention) then they may be co-enrolled in ARREST providing that this is allowed by the ongoing original study. Patients enrolled in ARREST should not be co-enrolled in new interventional trials of medicinal products during their 12 week follow-up, although they may be co-enrolled in observational studies.

Each patient should only be randomised in ARREST once: if they have a subsequent episode of *S. aureus* bacteraemia they are not eligible for re-randomisation.

# 5 TREATMENT OF PATIENTS

## 5.1 INTRODUCTION

All patients will receive the standard of care antibiotic to treat *S. aureus* bacteraemia that they would have received if they had not been enrolled in the ARREST trial. In addition, patients will be randomised to receive rifampicin or placebo (investigational medicinal product) as an extra medication for 2 weeks. Rifampicin/placebo for 14 days will be dispensed at randomisation from the site pharmacy in oral (capsule) formulations. At randomisation the study doctor will have stated whether or not they also require IV study drug (see below). Specific investigational medicinal product clinical trial stock will be prepared by a Clinical Trials Supplier (Sharp Clinical Services), identical in appearance and dosed and dispensed in the same way. The rifampicin/placebo will be given to patients as early as possible in the treatment of the bacteraemia but no later than 96 hours from the start of active antibiotic treatment (see inclusion criteria, Section 3.1 - Patient Inclusion Criteria p25). We hypothesise that rifampicin will improve outcome by enhancing early bacterial killing, therefore during the study we will carefully monitor when the study drug is started in relation to first active antibiotic treatment and subgroup analysis according to time-to-randomised treatment will be pre-specified (see Section 9.5 - Analysis Plan (Brief) p53).

## 5.2 TRIAL TREATMENT

### 5.2.1 ARM A

Active treatment with rifampicin for 14 days from randomisation (IV and/or oral according to patient status):

- Rifampicin oral 300 mg capsules (Sanofi-Aventis, UK)
  SPC: http://www.medicines.org.uk/emc/medicine/21223/SPC/Rifadin+300mg+Capsules/
- Rifampicin 600 mg for intravenous injection (Sanofi-Aventis, UK)
  SPC: http://www.medicines.org.uk/emc/medicine/6435

(see Section 5.3 - Treatment Schedule p31 below for details of dosing.)

### 5.2.2 ARM B

Treatment with matched placebo for 14 days from randomisation:

- Placebo oral 300 mg capsules containing cellulose (Sharp Clinical Services)
- Standard saline for intravenous injection

### 5.2.3 BLINDING ISSUES

Rifampicin capsules will be over- encapsulated by Sharp Clinical Services to make them indistinguishable from placebo. However, rifampicin for intravenous infusion comes as a vial of red powder which requires reconstitution with 10 ml of water for infusion with saline. The resulting fluid for intravenous infusion is orange. It is impossible to safely and reliably produce a red-powder placebo which will produce an identical orange infusion. Therefore, we accept that the nurse making up the intravenous drug for the infusion will not remain blind to the treatment. They will be instructed not to divulge the colour of the drug to the physicians caring for the patient. In addition, the infusion will be covered by an opaque bag to disguise the treatment.

Because of these blinding issues, and the inability to manufacture placebo for IV injection in a vial, active rifampicin for IV infusion will be dispensed from local NHS stores. *S. aureus* bacteraemia is

within the licenced indication for rifampicin. Approximately 10% of patients are likely to require IV study drug during the study, i.e. most patients will receive double-blind oral treatment only. IV rifampicin has to be reconstituted on the ward for immediate infusion, but it will be dispensed from the NHS Trust hospital pharmacy together with a 500ml bag of saline and an opaque bag cover. As far as possible the study doctors, study nurses, and other doctors caring for the patient will remain blinded. The infusion will be given over 2-3 hours, for as long as IV therapy is required, which will minimise the time of potential unblinding. For patients randomised to placebo, the pharmacist will send a 500ml bag of saline covered with an opaque bag direct to the ward ready for infusion. All patients will already be receiving their other *S. aureus* antibiotics intravenously, so no lines will be inserted merely for the purpose of providing placebo infusions. If a patient is receiving intravenous treatment in the ITU, the infusion volume may be altered (e.g. 250ml saline) in accordance with local standard practice and the SPC for Rifampicin 600 mg for intravenous injection.

A standardised label will be provided with the oral treatment pack (dispensed to all patients) to stick in the patient's medical notes to avoid inadvertent unblinding. A planned subgroup analysis will compare the impact of treatment in patients receiving oral treatment at randomisation vs IV treatment at randomisation, and also by terciles of C-reactive protein at randomisation, a marker of disease severity.

Rifampicin can turn urine (and tears/sweat) reddish-orange. It is impossible to safely replicate this effect with a placebo; therefore urine discolouration will be a potential source of unblinding, particularly of the patient. There is, however, considerable inter- and intra-individual variability in rifampicin's effect on urine colour. In some patients, the colouration is slight and can be hard to distinguish from the dark, concentrated urine frequently observed in acutely unwell patients. In many, the orange urine colour becomes less marked over time. In addition, the opportunity for physicians to examine the urine at the bedside will only occur in patients with urinary catheters. Catheters will not be required by all patients and are usually removed at the earliest opportunity. We will also limit the opportunity for physicians to inspect urine by ensuring the catheter bags are emptied regularly and urine it is not allowed to accumulate in large volumes.

## 5.3 TREATMENT SCHEDULE

The dose of rifampicin/placebo will be prescribed according to the patient's weight:

- those <60kg will receive 600mg every 24h
- those ≥60kg will receive 900mg every 24h

Rifampicin/placebo will be given by oral or intravenous route, according to the attending physician's preference and the patient's status. Oral rifampicin has excellent bioavailabilty with oral administration achieving comparable plasma concentrations to the intravenous route. Therefore, provided a patient can swallow safely, most physicians will elect to use rifampicin orally. We anticipate around 90% of doses will be given by mouth. When possible, the drug should be given before food, although this can be difficult in very sick patients and is therefore not mandatory within this protocol. Patients may start taking IV rifampicin/placebo and then move to the oral formulation when they can swallow safely. Please note that if a patient requires a Percutaneous endoscopic gastrostomy (PEG) tube then it is not permissable for the IMP capsules to be opened and administered via PEG.

It is important, however, to allow intravenous administration to very sick patients who may not be able to swallow or absorb tablets (see above). Additional intravenous catheters will not be required to administer the study drug as standard antibiotic therapy (with a beta-lactam or glycopeptide) is

always given intravenously. Oral doses can be given once or twice daily, according to clinician and patient preference, and subgroup analysis according to initial oral dosing frequency (elicited at randomisation) will be pre-specified (see Section 9.5 - Analysis Plan (Brief) p53). If taken twice daily, 900mg daily (3 capsules) should be taken as unequal divided doses (600mg am, 300mg pm): as rifampicin can also be taken once daily, this will provide adequate exposure. The study treatment will be given for 14 days, unless fewer than 14 days of standard antibiotic therapy is planned, in which case rifampicin/placebo will be given until standard antibiotic treatment ends.

### 5.3.1 DISPENSING

Sharp Clinical Services (http://www.sharpclinical.com) (formerly Bilcare GCS) will make up and label individual-patient blinded treatment packs with ARREST trial numbers, containing either active drugs or identical placebo capsules sufficient for 14 days treatment according to the prespecified randomisation list. Active drug or placebo for intravenous injection will only be administered if requested by the trial physicians, and will be dispensed by the local pharmacist according to a site-specific treatment allocation list stored securely with the treatment packs in the local NHS pharmacy. Based on (8), between 5-15% of patients will require any IV therapy, and very few will require >5 days.

Sharp Clinical Services is licensed by the MHRA to manufacture and test investigational materials for clinical trials. Randomisation will be stratified by clinical site and so blinded drug (in fully made-up and labelled treatment packs) will be pre-shipped to local pharmacies from where it will be dispensed to enrolled patients on the basis of allocated trial numbers. As per the SPC for Rifampicin oral 300 mg capsules, the treatment packs must be kept in pharmacy below 25°C. There is no requirement for temperature monitoring of treatment packs after they are dispensed from pharmacy.

After randomisation, the ward or ARREST research nurse will take the completed ARREST prescription form to the site pharmacy who will dispense the trial-number specific rifampicin/placebo pack containing the oral (capsule) formulation for 14 days as above. Intravenous treatment will also be given if requested post-randomisation following the same procedure. On no account should any drug assigned to a patient be used by anyone else. Unused drug must be returned to the site pharmacy immediately if a patient withdraws from treatment. The time that each patient started blinded rifampicin/placebo should be documented in the patient's clinical notes and added to the day 3 CRF in order to enable subgroup analysis according to time from initiation of antibiotics to initiation of randomised treatment.

All drug dispensed at and returned to the site pharmacy should be documented on a site Accountability Log, maintained by a named person (trial pharmacist or research nurse). The designated trial pharmacist/nurse will, on receipt of supplies prior to the commencement of the trial, conduct an inventory and complete a receipt. Inventories will be conducted monthly, and logs returned to MRC CTU at UCL. Procedures for drug shipping, labelling, accountability, temperature monitoring and destruction will be detailed in the ARREST working practice documents. MRC CTU at UCL will monitor drug accountability at site visits.

### 5.3.2 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

Toxicity will be managed in all randomised groups according to standard clinical practice. Blood tests additional to those described in the trial schedule may be requested at any time for clinical management of the patient. In some situations, changes in the patient's condition may mean that the dose of rifampicin should either be reduced or stopped altogether. Wherever possible, this should be done without unblinding. Unblinding should only be performed when knowledge of the

allocated treatment has a direct bearing on clinical management. Patients will not be put at any additional risk by trial randomisation, as any patient who develops a suspected adverse drug reaction to study drug will be managed as if they were receiving rifampicin, and study drug discontinued.

The most important rifampicin toxicity is liver impairment, although serious hepatic toxicity is rare (<1% of patients). The study drug (rifampicin/placebo) should typically be withdrawn without unblinding if significant liver toxicity is observed (blood AST/ALT > 5x upper limit of normal (ULN)) without other probable causes, and must be withdrawn for grade 4 liver toxicity (blood AST/ALT > 10xULN) regardless of probable cause. The dose of study drug can be reduced if less severe liver dysfunction occurs according to the judgement of the treating physician. Other medications (including other antibiotics) should be continued at the discretion of the treating physician. Rifampicin-related hepatic toxicity requires no specific treatment other than its withdrawal, and therefore knowledge of whether the patient was receiving rifampicin or placebo is not mandated for patient management. All dose modifications, interruptions and discontinuations should be reported in the follow-up CRFs.

Rifampicin has a number of other uncommon side-effects, which include anorexia, nausea, vomiting and diarrhoea; headache and drowsiness; haemolytic anaemia, thrombocytopenic purpura, disseminated intravascular coagulation and leucopenia; flushing, urticaria and rashes; and a flu-like syndrome with fever (although this is usually associated with administration twice or three times/week).

#### 5.3.2.A Specific situations in which rifampicin/placebo should be discontinued before 14 days

Rifampicin/placebo should be discontinued before 14 days in two specific situations:

- where other antibiotics being used to treat *S. aureus* bacteraemia are stopped before 14 days after randomisation. This is to prevent rifampicin being given as monotherapy which could theoretically increase the risk of resistance.
- where results from *S. aureus* susceptibility testing become available after the patient has been randomised and initiated rifampicin/placebo and indicate resistance to rifampicin (on standard British Society for Anti-microbial Chemotherapy disc testing or by Vitek testing). This is to prevent any toxicity from an additional but ineffective drug being used. Primary rifampicin resistance is expected in <1% enrolled patients based on current observational study data.

Other general discontinuation criteria are considered in Section 5.6 - Protocol Treatment Discontinuation p34.

### 5.4 OVERDOSE OF TRIAL MEDICATION

The maximum licenced daily dose of rifampicin is 1200mg. Non-fatal acute overdoses have been reported in adults with doses ranging from 9000mg to 12000mg. The clinical consequences have been confusion or delirium, hepatitis, nephritis, peripheral neuritis and red man syndrome. Treatment is supportive, following withdrawal of the drug, and therefore management following any overdose will be identical regardless of randomised arm, and would not be a reason for unblinding. Given the study drug will be adminstered by ward nurses, the risks of overdose will be extremely small.

## 5.5 UNBLINDING

Unblinding will generally be discouraged during treatment. If, however, in the opinion of the local clinician, it is important for good clinical care to unblind treatment (for instance because of a severe hepatic reaction that may have other causes that require investigation, or in order to prescribe hydrocortisone as adjunctive steroid treatment to dose-escalating noradrenaline in the case of septic shock (where the dose is doubled if the patient is also receiving active rifampicin)), the request will be discussed with the site Principal Investigator (PI) then the Chief Investigator (CI). The requesting clinician should be able to state alternative courses of management if the patient is found to be receiving rifampicin versus placebo. If agreed that this information is essential for best management of the patient, the unblinding code will be provided by the Trial Statistician (or other delegated statistician) at MRC CTU at UCL. This individual will then contact the investigator at the clinical centre directly to inform them of the treatment allocation of the patient. All analyses will be by intention-to-treat, regardless of subsequent changes in treatment.

Generalized clinical deterioration is not sufficient for unblinding, given equipoise about the evidence base supporting the use of rifampicin regardless of clinical severity.

All instances of unblinding will be recorded and reported to the DMC and TSC. All patients will be unblinded by MRC CTU at UCL after trial closure and database lock via their GPs. The quality of the blinding will be assessed by eliciting physician and patient views on which treatment they thought they had received at the end of the 12 week visit.

### 5.5.1 EMERGENCY UNBLINDING

In an emergency please call the Chief Investigator on 07818 040689. If the Chief Investigator is unavailable please call MRC CTU at UCL on 07746 795024.

### 5.5.2 UNBLINDING BY THE MRC CTU AT UCL

For general questions about unblinding please call the ARREST Trial Manager on 020 7670 4937.

If unblinding is required in order to decide whether or not a reported SUSAR should be filed with the regulatory authorities (see Section 7.4 - MRC CTU at UCL Responsibilities p47) then the Trial Manager will, after discussion with the Chief Investigator, inform the individual with access to the randomisation allocation list. This individual will be provided with all completed and signed documentation necessary for reporting the event as a SUSAR. If the product administered to the patient is found to be rifampicin then the individual would report the case as a SUSAR to the MHRA and to the MREC. If the product administered was placebo then the individual will reclassify the event as an SAE and it will not be reported. Neither the Trial Manager, nor the Chief investigator nor the site Principal Investigator will be informed of the results of the unblinding.

## 5.6 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. However, an individual patient may stop treatment early or be stopped early for any of the following reasons:

- Patient no longer receiving standard antibiotic treatment for *S. aureus* bacteraemia (see Section 5.3.2 above)
- *S. aureus* identified as resistant to rifampicin on susceptibility testing (see Section 5.3.2 above)
- Unacceptable toxicity or adverse event

- Intercurrent illness that prevents further treatment
- Any change in the patient's condition that justifies the discontinuation of treatment in the treating physicians opinion and after discussion with the site PI (including use of contraindicated concomitant medications, see Section 5.10.1 p36)
- Inadequate compliance with the protocol treatment in the judgement of the treating physician
- Withdrawal of consent for treatment by the patient

As the patient's participation in the trial is entirely voluntary, they may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled, including if consent was originally given by a LR and the patient has now regained capacity to consent for themselves. Although the patient is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the patient's rights.

Patients should remain in the trial for the purpose of follow-up and data analysis (unless the patient withdraws their consent from all stages of the trial). If a patient is withdrawn from follow-up, refer to Section 6.6 - Early Stopping of Follow-up p41. Data will be kept and included for patients who stop follow-up early.

## 5.7 ACCOUNTABILITY & UNUSED DRUGS

Investigational Medicinal Product (IMP) will be centrally packed by Sharp Clinical Services and a supply sent to the hospital pharmacy at each of the participating sites. The hospital pharmacy will document receipt of supplies and returns.

IMP accountability will be maintained and monitored by site staff and MRC CTU at UCL respectively according to the ARREST working practices. At the earliest of 14 days after randomisation or end of treatment with rifampicin/placebo, nurses will be asked to return any unused drug to the site pharmacy. At the end of the trial all non-dispensed IMP will be checked against the inventory before disposal on site according to local pharmacy guidelines and applicable regulations. Documentation of disposal will be provided to MRC CTU at UCL.

## 5.8 COMPLIANCE & ADHERENCE

As the intervention will start immediately following randomisation, suitable patient information and fully informed consent proceedures will ensure that participants understand the trial requirements. Therefore, any non-compliance will likely be a consequence of the intervention itself (e.g. drug intolerance or toxicity) which would also likely occur if it were incorporated within clinical practice, i.e. non-compliance will likely be part of the pragmatic strategy being evaluated and an intention-to-treat comparison will therefore incorporate the level of non-compliance as would be anticipated in general clinical practice.

The study drug will be given in hospital by ward nurses alongside other standard antibiotic therapy (which will be intravenous in the vast majority of cases) and other regular medication. Few problems with compliance and adherence are therefore envisaged. Compliance and adherence to the 2-week study treatment regimen will be assessed by visits to the patient by the study team on days 3, 7, 10 and 14 of treatment through review of the medication charts. Missed doses will be detected, if they do occur, and recorded in the CRF. As part of routine clinical practice, no patient will be discharged whilst still receiving IV rifampicin/placebo - relatively few patients will be discharged before 14 days,

but if this were to occur patients would already be receiving oral formulations. If a patient is discharged before 14 days they will be asked to return all unused pills at the 12 week visit.

All efforts must be made to ensure that the patient does not receive more than 14 days of trial treatment. When a patient does receive more that 14 days of trial treament in error, if additional doses are given for more than 24 hours (i.e. 15 days) then this must be reported as a protocol deviation.

## 5.9 TREATMENT DATA COLLECTION

Every antibiotic prescribed (including rifampicin/placebo), its dose, frequency, route of administration, and duration will be recorded in the CRF. Antibiotics given before randomisation for the treatment of this *S. aureus* bacteraemia episode will also be documented, as will all antibiotics received through 12 weeks follow-up.

The time infected foci (e.g. intra-venous catheters) were removed will be documented. All surgical interventions (drainage of pus from infected sites, for example) performed as part of the management of the infection will be recorded.

## 5.10 NON-TRIAL TREATMENT

The choice and duration of standard antibiotic therapy which accompany the IMP will be left to the attending physician, but is expected to be either a beta-lactam (e.g. flucloxacillin) or a glycopeptide (vancomycin or teicoplanin). Daptomycin and linezolid are the other alternatives, although current data from the trial sites indicate <1% receive daptomycin and around 5% receive linezolid as initial first-line therapy. A pre-specified subgroup analysis will be conducted by standard antibiotic therapy, at a class level, and according to individual drugs where these are used by >10% of the trial population. If the physician wishes to use other antibiotics (or rifampicin) after 14 days (the study drug duration), this will be open-label, but recorded on CRFs.

Treatment with drugs with potentially important interactions with rifampicin (e.g. warfarin) will also be documented.

### 5.10.1 MEDICATIONS PERMITTED

Physicians are permitted to use any antibiotic of their choice – other than the trial drug, rifampicin - in combination with the study drug and by any route. All other concomitant medications essential for patient management are permitted at enrolment, subject to the exclusion criteria of no contraindications to the use of rifampicin in the judgement of the attending clinician (see Section 3.2 - Patient Exclusion Criteria p26). If use of a concomitant medication that cannot safely be used with rifampicin becomes essential after randomisation, then the IMP should be stopped and the concomitant medication used without unblinding.

### 5.10.2 MEDICATIONS NOT PERMITTED

None.

### 5.10.3 MEDICATIONS TO BE USED WITH CAUTION

Rifampicin induces the hepatic metabolism of many drugs and can result in their sub-therapeutic concentrations. The recruiting infection specialists will be responsible for identifying clinically important interactions and ensuring appropriate action is taken to reduce the risks to patients; this

may include judging patients receiving these medications as not eligible to join the trial. For example, the anti-coagulant effect of warfarin is reduced by rifampicin. The clinical importance of this effect varies according to the indication for warfarin anti-coagulation. The risks of rifampicin-induced anti-coagulation failure in patients with a prosthetic heart valve (valve thrombosis) are far greater than for patients on warfarin for a previous deep vein thrombosis. Therefore, whether rifampicin should be given to those on warfarin, or any other medication with which it interacts, should be assessed on a case-by-case basis by the recruiting physician. If the physician is uncertain whether the interaction can be safely managed, the patient should not be enrolled.

### 5.10.4 TREATMENT AFTER 14 DAYS

Treatment will be at the discretion of the responsible physician. If antibiotic treatment is continued beyond 14 days, the antibiotics given (with dose and frequency of administration) will be recorded in the CRF.

Rifampicin may be used open-label after 14 days if required in the judgement of the treating clinician. Situations in which this would be considered appropriate medical treatment (ie failure of initial therapy) will almost invariably already be recorded as secondary endpoints.

## 5.11 LOSS OF CAPACITY DURING THE TRIAL

As defined by the Medicines for Human Use (Clinical Trial) Regulations 2004, consent from an adult to participate in a trial remains valid after loss of capacity, providing the trial is not significantly altered. In this situation, trial staff will consult with carers and take note of any signs of objection or distress from the patient, and will consider withdrawing the patient from the trial if any objections to their continued participation are raised.

# 6 ASSESSMENTS & FOLLOW-UP

All participants will be followed by the site study teams for 12 weeks for evaluation of all-cause mortality, morbidity and toxicity. Subsequent follow-up will be electronic through hospital records (consent will be sought for this together with consent for trial participation, see Appendix III - Trial Consent forms p89). To assess the outcome measures, patients will be visited on the ward by the site PI, one of their clinical team (e.g. Specialist Registrar), or a research nurse on day 3, 7, 10 and 14, and then weekly whilst still in hospital through 12 weeks (see Trial Assessment Schedule page viii). The day 3, 7, 10 and 14 visits should occur within ±1 days wherever possible, and the weekly visits in hospital within ±2 days (allowing for weekends and other necessary procedures in very sick patients).

All those recording clinical data will be identified by each site PI, receive appropriate training and sign the Delegation Log. Clinical data will be obtained through consultation with the patient, their medical team, or their medical records. Laboratory measures and resource utilisation will be extracted from patient notes/electronic records; study nurses will administer the EQ-5D to patients. Those patients discharged before 12 weeks will be managed and followed-up through each site's infectious diseases out-patient clinic. Final follow-up at 12 weeks will be either by a ward visit (if the patient is still admitted to hospital) or by a clinic visit with interview and clinical assessment. In the event that the patient is unable to attend clinic, the follow-up visit can take place over the phone. The 12 week visit should occur between 11 and 20 weeks from randomisation, i.e. a window from [-1,+8] weeks is allowed to avoid losing important follow-up data. All data will be recorded on (electronic) eCRFs (developed from those currently in use in our observational study).

Any additional visits or diagnostic/laboratory tests needed for patient management should occur as required at the discretion of the treating phyisician. Results from these investigations should be recorded on ARREST CRFs, but only the specified investigations below are required in all patients.

## 6.1 TRIAL ASSESSMENT SCHEDULE

See page viii for the Trial Assessment Schedule.

At each main clinical assessment (days 0, 3, 7, 10, 14, weekly until discharge, day 84 (final outpatient visit)), the following will be undertaken:

- Assessment of new or on-going foci of infection together with arrangements to identify, remove or drain the focus if necessary
- Assessment of clinical treatment response, including whether the patient was febrile (>37.5$^0$C) in the previous 24 hours
- Record all grade 3 or 4 adverse events, all serious adverse events, and all adverse events of any grade leading to modification of rifampicin/placebo dose or its interruption/early discontinuation. The severity and likely relationship of these adverse events to rifampicin/placebo will be documented by a physician. Any drug interactions leading to dose modification of any drug (including concomitant medications) will also be recorded.
- Assessment of adherence to rifampicin/placebo (missed pills, early termination of IV infusion)
- Assessment of resource utilisation (medications, procedures, laboratory tests and other relevant resource use categories) (not day 3, 10)

EQ-5D will be administered on days 0, 7, 14 and 84 (final outpatient visit) (see Appendix V - EQ-5D questionnaire p94).

Blood cultures will be repeated on days 0, 3 and 7 to assess duration of bacteraemia in all patients as persistent bacteraemia is strongly predictive of worse outcome. Blood cultures may be taken at any other timepoints necessary for clinical management: but must additionally be taken if potential treatment failure is suspected (e.g. in patients who still have a positive blood culture on day 7 and in whom transoesophageal echocardiography (TOE) is being considered) or where *S. aureus* bacteraemia recurrence is suspected. C-reactive protein will be measured on days 0, 3, 10 and 14 to assess treatment response. ALT, bilrubin, alkaline phosphatase will be assessed on days 3 and 10 to evaluate liver toxicity. Full blood count will be measured at baseline in all patients as total white cell count/total neutrophils may be important baseline prognostic determinants. EDTA plasma (2.5mls of blood) and PAXgene blood RNA tube (2.5mls of blood) will be taken from patients on day 0 stored for later DNA/RNA extraction where consent has been provided for this. If a patient has already been discharged from hospital before day 7, 10, or 14, these additional investigations requiring a blood draw (culture, CRP, ALT, ALP, bilirubin, serum storage) are not required so patients should not be asked to attend ARREST specific outpatient appointments on these days, but to return at 12 weeks only. If however a patient is attending outpatient appointments for other reasons then please collect blood samples for these visits if possible.

In patients recruited to the PK/PD substudies (see Section 11.1 p56) plasma from lithium heparin tubes will be stored for assessment of plasma concentrations of rifampicin, vancomycin, teicoplanin and flucloxacillin for PK/PD analysis. Blood cultures will be taken more frequently in those participating in the PK/PD studies as the kinetics of bacterial kill in the blood will be a key endpoint in the PD analysis. In addition, serum creatinine will be measured on days 0, 3 and 10 in those recruited to the intensive study, and on day 0 alone in the sparse study. This is because renal function influences the exctretion of glycopeptide and beta-lactam antibitoics. Peripheral blood mononuclear cells and neutrophil fractions from blood taken for culture in intensive PK/PD study participants will be frozen and stored for later characterisation by flow cytometry.

Participants in all groups may undergo all necessary diagnostic tests for clinical management of illness. The timing and results of all radiographic investigations (including echocardiography) will be recorded. If treatment failure or *S. aureus* bacteraemia recurrence are suspected then repeat blood cultures should be performed together with a clinical assessment and EQ-5D.

## 6.2 PROCEDURES FOR ASSESSING EFFICACY

The trial's primary outcome is:

- death or microbiologically confirmed treatment failure or disease recurrence (bacteriological failure) up to 12 weeks from randomisation

This outcome measure will be assessed by visiting the patient on days 3, 7, 10, 14, and weekly thereafter until discharge from hospital, and the final clinical assessment 12 weeks after recruitment (either by a ward visit (if the patient is still admitted to hospital) or a clinic visit). If the patient fails to attend the 12-week follow-up visit they will be contacted by telephone. The patient's GP may also be contacted; consent to contact the patient and their GP will be obtained.

The definition of microbiologically confirmed treatment failure is:

(1) symptoms and signs of infection ongoing for longer than 14 days from randomisation AND

(2) the isolation of same strain of *S. aureus* (confirmed by genotyping) from either blood or another sterile site (e.g. joint fluid, pus from tissue) indicating blood-born dissemination of the bacteria

The definition of microbiologically confirmed disease recurrence is :

(1) the isolation of the same strain of *S. aureus* from a sterile site after >7 days of apparent clinical improvement.

Outcome measures include *S. aureus* infection of sterile sites other than just blood, because such disseminated infection can be the consequence of failure to treat initial infections adequately. Asymptomatic bacteraemia without any sign or symptom of infection is not considered failure. Additional blood cultures should be requested as soon as the site PI/study doctor suspect treatment failure or recurrence (see Trial Assessment Schedule page viii). All bacterial isolates (initial and all subsequent) from patients randomised in the trial will be genotyped by multi-locus sequence (37) and spa-typing (38) and tested for susceptibility to rifampicin.

The secondary efficacy outcome measures are:

- all cause mortality up to 14 days
- death or clinically defined treatment failure or recurrence by 12 weeks
- duration of bacteraemia
- development of rifampicin resistance.

Mortality should be reported on an SAE form, see Section 7.1 p43 below.

Clinically defined treatment failure or recurrence will be assessed clinically in the same manner as microbiologically confirmed treatment failure; however, microbiological confirmation will not be required (for example, patients who fail treatment clinically but where blood cultures were not done). Clinically defined treatment failure/recurrence will primarily be determined by radiological evidence for an on-going or new active infection focus by 12 weeks and the requirement for on-going or new antibiotic therapy.

Site PIs will report all potential treatment failures/recurrences and they will be adjudicated as trial endpoints by review of each patient's clinical progress by an independent endpoint committee blind to the treatment allocation (see Section 15.5 - Endpoint Review Committee p69).

Blood cultures will be taken on days 3 and 7 following randomisation to assess duration of bacteraemia. It is essential that, at minimum, sensitivity to rifampicin (and ideally a general antibiogram) be repeated on the day 3 and 7 blood cultures in order to assess the important secondary endpoint, development of rifampicin resistant *S. aureus* in all subsequent *S. aureus* isolates grown at scheduled timepoints or at treatment failure, as it is unlikely to be detectable until treatment fails or the disease recurs and *S. aureus* can be re-cultured from blood or another sterile site.

CRP will be measured longitudinally as a continuous measure of response to infection, which can also be compared with blood drug levels and with duration of bacteraemia.

## 6.3 PROCEDURES FOR ASSESSING SAFETY

Liver function tests will be performed twice whilst on rifampicin/placebo (day 3 and 10) to assess laboratory safety parameters. Additional safety blood tests or investigations may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Grade 3 and 4 and serious adverse events will be elicited at the regular clinical assessments, through consultation with the patient, their medical team, or their medical records. All such adverse events will be reported on CRFs, together with adverse events of any grade leading to modification of rifampicin/placebo dose or its interruption/early discontinuation. All such adverse events (clinical and laboratory) will be graded using the Common Toxicity Criteria (CTC) grading scale v4.0 (see Appendix VI - Toxicity Gradings and Management p95) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Serious adverse events will be defined according to ICH GCP, and will be reported to the MRC CTU at UCL according to standard timelines (see Section 7 - Safety Reporting p43). All SAEs should be reported on study CRFs, unless they are specifically related to the *S. aureus* bacteraemia episode for which the patient was originally admitted (in which case they will be reported as infection-related events). The severity and likely relationship of any adverse events to rifampicin/placebo will be documented by a doctor. All reported adverse events will be coded centrally at the MRC CTU at UCL using the Medical Dictionary for Regulatory Activities (MedDRA).

All modifications to rifampicin/placebo dose or administration will be recorded as will all significant drug interactions requiring modification of study and non-study medication.

## 6.4 PROCEDURES FOR ASSESSING QUALITY OF LIFE

Patients will be asked to complete the EuroQol-5D questionnaire (EQ-5D) at days 0, 7, 14 and 84 providing they have the capacity to do this at the visit (see Appendix V - EQ-5D questionnaire p94).

## 6.5 OTHER ASSESSMENTS

Other assessements performed within the trial will be the healthcare-related costs of *S. aureus* bacteraemia and the evaluation of health-related quality of life using the EuroQol-5D questionnaire (EQ-5D). These assessments will be used further to inform the cost effectiveness of adjunctive rifampicin and relevant antibiotic regimens for *S. aureus* bacteraemia.The trial will measure all the healthcare-related costs of patients in the trial, starting from when the first positive blood culture was taken and continuing for the duration of follow-up. Information on hospitalisation costs (including procedures, laboratory tests and concomitant medications) will be collected at the regular clinical assessments, and data on other healthcare resource utilisation (post-discharge outpatient visits, medications, and procedures) will be collected at the 12 week visit.

Within trial assessments of health related quality of life (using the EQ5D) will also be used in the economic analysis. EQ5D scores will be used to weight lifetime lived by its quality; the EQ5D tariff developed for the UK will be used to derive the scores from the participants responses to the EQ5D's descriptive system [39]. The cost effectiveness analysis will thus use QALY (Quality Adjusted Life Years) as the outcome measure (further details in Section 11.1 – Ancilliary studies).

## 6.6 EARLY STOPPING OF FOLLOW-UP

If a patient chooses to discontinue their trial treatment (rifampicin/placebo), they should always be followed up (providing they are willing) and they should be encouraged not to leave the whole trial. If they do not wish to remain on trial follow-up, however, their decision must be respected and the patient will be withdrawn from the trial completely. The MRC CTU at UCL should be informed of this on the Withdrawal of Consent CRF. The reason for the patient withdrawing should be ascertained

wherever possible. Prior to withdrawing completely from the trial, the patient will be asked to have assessments performed as appropriate for the final 12 week visit although they would be at liberty to refuse any or all individual components of the assessment.

If a patient withdraws from the trial, the medical data collected during their previous consented participation in the trial will be kept and used in analysis. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion). If consent for future use of stored samples already collected is refused, then all such samples will be destroyed following the policies of the institution where the samples reside at the time (local or central storage).

Patients may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial.

Patients who stop trial follow-up early will not be replaced, as the total sample size includes adjustment for losses to follow-up.

Patients will be followed up 5 years after trial closure through local electronic NHS records (consent will be sought for this).

## 6.7 LOSS TO FOLLOW-UP

In the statistical analysis, a patient will be classified as 'lost to follow-up' if they have not been seen at the 12 week final visit (within a [-1,+8] week window). Any patient who is discharged from hospital before 12 weeks but does not attend the 12 week visit will be traced through their General Practitioner (GP).

## 6.8 ASSESSMENTS AT TRIAL CLOSURE

The trial will end after the final 12 week visit of the last patient to be randomised. At the end of the trial, vital status of all participants will be ascertained from electronic NHS records (consent will be sought for this, see Appendix III - Trial Consent forms p89).

The only situation in which the trial is likely to be stopped early would be following a recommendation from the Data Monitoring Committee (see Section 9.4 - Interim Monitoring & Analyses p53).

# 7 SAFETY REPORTING

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. Section 7.1 - Definitions lists definitions, Section 7.3 - Investigator Responsibilities gives details of the investigator responsibilities and Section 7.4 - MRC CTU Responsibilities provides information on MRC CTU at UCL responsibilities.

## 7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial protocol. These definitions are given in Table 7.1: Definitions.

**Table 7.1: Definitions**

| TABLE | DEFINITION |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a patient or clinical trial subject to whom an investigational medicinal product has been administered including occurrences that are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | Any untoward and unintended response to an investigational medicinal product related to any dose administered. |
| Unexpected Adverse Reaction (UAR) | An adverse reaction, the nature or severity of which is not consistent with the information about the investigational medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product. |
| Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) | Respectively any adverse event, adverse reaction or unexpected adverse reaction that:<br>▪ Results in death<br>▪ Is life-threatening*<br>▪ Requires hospitalisation or prolongation of existing hospitalisation**<br>▪ Results in persistent or significant disability or incapacity<br>▪ Consists of a congenital anomaly or birth defect<br>▪ Is another important medical condition*** |

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

### 7.1.1 Medicinal Products

An investigational medicinal product is defined as the tested investigational medicinal product (IMP) and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision). This therefore includes

- rifampicin
- placebo

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

### 7.1.2 Exempted Adverse Events

In the context of this trial Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms
- Disease-related events that are not fatal

### 7.1.3 Disease-related Events

Dissemination of *S. aureus* to infect distant, and sometimes multiple, sites is a common clinical complication of *S. aureus* bacteraemia. These events are important trial endpoints as we hypothesise they will be prevented by adjunctive rifampicin. They will be detected and documented by the trial team through regular, repeated clinical review of the study patients and form part of primary and secondary efficacy endpoints. These events, and their associated signs and symptoms, should therefore not be reported as adverse events.

Death should always be reported as a (serious) adverse event, regardless of cause.

### 7.1.4 Other Study-specific Requirements

Rifampicin has the potential to interact with a large number of commonly used drugs. Therefore, investigators will need to be particularly vigilant pre- and post-enrollment to ensure all potential interactions are highlighted and managed appropriately. All potential interactions, and any arising adverse clinical consequences, will be documented in the CRF.

## 7.2 OTHER NOTABLE EVENTS

### 7.2.1 PREGNANCY

There is considerable experience of using rifampicin for the treatment of tuberculosis in pregnancy; the 2010 World Health Organisation tuberculosis treatment guidelines state that rifampicin is safe in all trimesters of pregnancy (40). Therefore, pregnant patients can be enrolled in the trial if they satisfy the eligibility criteria. Given the acute nature of *S. aureus* bacteraemia, it is extremely unlikely that any patient would become pregnant during the 12 week follow-up. However, were this to occur the woman would be followed until term or termination to determine foetal outcome, and any congenital abnormality would be reported as an SAE.

## 7.3 INVESTIGATOR RESPONSIBILITIES

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the toxicity (symptoms) section of the Follow-up Form and sent to the MRC CTU within 31 days.

SAEs and SARs should be notified to the MRC CTU at UCL within 24 hours of the investigator becoming aware of the event.

### 7.3.1 INVESTIGATOR ASSESSMENT

#### 7.3.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definition given in Table 7.1: Definitions. If the event **is serious and not only related to the original *S. aureus* infection, or is fatal**, then an SAE Form must be completed and the MRC CTU at UCL notified within 24 hours.

#### 7.3.1.B Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in Appendix VI - Toxicity Gradings and Management p95.

#### 7.3.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 7.2: Assigning Type of SAE Through Causality. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

**Table 7.2: Assigning Type of SAE Through Causality**

| RELATIONSHIP | DESCRIPTION | SAE TYPE |
|---|---|---|
| Unrelated | There is no evidence of any causal relationship | Unrelated SAE |
| Unlikely | There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment). | Unrelated SAE |
| Possible | There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments). | SAR |
| Probable | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. | SAR |
| Definitely | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. | SAR |

If an SAE is considered to be related to trial treatment and drug is stopped or the dose modified, refer to Section 5.3.2 - Dose Modifications, Interruptions & Discontinuations p32.

### 7.3.1.D Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), the investigator must assess the expectedness of the event. An unexpected adverse reaction is one not previously reported in the current Summary of Product Characteristics (SPC) at the time the event occurred, or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in Table 7.1: Definitions. If a SAR is assessed as being unexpected, it becomes a SUSAR.

Investigators should always check the current version of the SPC. Expected toxicities associated with rifampicin are:

- ***Cutaneous reactions*** which are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically they consist of flushing and itching with or without a rash. Urticaria and more serious hypersensitivity cutaneous reactions have occurred but are uncommon. Exfoliative dermatitis, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyell's syndrome and vasculitis have been reported rarely.
- ***Gastrointestinal reactions*** consist of anorexia, nausea, vomiting, abdominal discomfort, and diarrhoea. Pseudomembranous colitis has been reported with rifampicin therapy.
- ***Hepatitis*** can be caused by rifampicin and liver function tests may become elevated
- ***Central Nervous System*****:** Psychoses have been rarely reported.
- Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs. Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.
- Disseminated intravascular coagulation has also been rarely reported.

- Eosinophilia, leucopenia, oedema, muscle weakness and myopathy have been reported to occur in a small percentage of patients treated with rifampicin.
- Agranulocytosis has been reported very rarely reported.
- Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

#### 7.3.1.E Notification

The MRC CTU at UCL should be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify the MRC CTU at UCL of all SAEs occurring from the time of randomisation until the patient finishes their 12 week follow-up. SARs and SUSARs must be notified to the MRC CTU at UCL until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

### 7.3.2 Notification Procedure

- The SAE CRF on the ARREST database (https://macro.ctu.mrc.ac.uk/macro) must be completed by the investigator (the consultant named on the Signature List and Delegation of Responsibilities Log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed by a member of the site trial team. The responsible investigator should subsequently check the SAE CRF, make changes as appropriate, and sign as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

- The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting and why the event is considered serious.

- The SAE CRF must be completed and an email sent to the MRC CTU at UCL to notify them: **mrcctu.arrest@ucl.ac.uk** .

- If the ARREST database is not available, the Emergency Paper SAE CRF should be completed and faxed to 020 7670 4817 or emailed to mrcctu.arrest@ucl.ac.uk

- Follow-up: patients must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. A further SAE Form, indicated as 'Follow-up' should be completed as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence and should be deleted from any test results.

- Staff should follow their institution's procedure for local notification requirements.

## 7.4 MRC CTU at UCL Responsibilities

Medically-qualified staff at the MRC CTU at UCL and/or the Chief Investigator (or a medically-qualified delegate) will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU at UCL is undertaking the duties of trial sponsor with regard to safety reporting and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and the research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the MRC CTU at UCL becoming aware of the event; other SUSARs must be reported within 15 days.

The MRC CTU at UCL will also keep all investigators informed of any safety issues that arise during the course of the trial and will submit Development Update Safety Reports to Competent Authorities (Regulatory Authority and Ethics Committee).

# 8 QUALITY ASSURANCE & CONTROL

## 8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of ICH GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the Research Governance Committee (RGC) and has led to the development of a Quality Management Plan (QMP), which will be kept separately.

The safety profile of rifampicin is well-known and acceptable, given the potential benefits. Rifampicin has been given to large numbers of patients worldwide in clinical trial settings and in clinical practice, predominantly for far longer (6-9 months) than proposed here (2 weeks) for the treatment of tuberculosis. The trial will be recruiting sick patients, but site investigators have considerable experience with this population and have already been collecting data for an observational study. This will minimise the risks to the patients and the trial. A detailed risk assessment will be conducted prior to starting the trial.

## 8.2 CENTRAL MONITORING AT MRC CTU AT UCL

Data will be entered at each site onto electronic Case Report Forms (eCRFs). Data stored on the central database will be checked at MRC CTU at UCL for missing or unusual values (range checks) and checked for consistency within patients over time. If any such problems are identified, the site will be contacted and asked to verify or correct the entry. MRC CTU at UCL will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

Other essential trial issues, events and outputs will be detailed in the Data Management, Monitoring and Quality Management Plans that are based on the trial-specific Risk Assessment.

## 8.3 ON-SITE MONITORING

Staff from MRC CTU at UCL will visit clinical sites to validate and monitor data. The frequency, type and intensity of routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring and Quality Management Plans. These plans will also detail the procedures for review and sign-off.

A site initiation visit or WebEx teleconference call will be conducted for each study site by staff from the MRC CTU at UCL. All essential site staff including the PI, lead pharmacist and lead research nurse must be in attendance. The initiation training will include training in the administration of blinded study drug, as well as the trial procedures. All microbiology laboratories will be required to provide evidence of certification before site initiation. Monitoring will then be carried out approximately annually at each site by MRC CTU at UCL staff. The monitoring will adhere to the principles of ICH GCP and the Monitoring Plan.

Monitors will:

- verify completeness of the Investigator Site File
- confirm adherence to protocol
- review eligibility verification and consent procedures
- look for missed clinical event reporting
- verify completeness, consistency and accuracy of data being entered on CRFs
- evaluate drug accountability
- provide additional training as needed

The monitors will require access to all patient medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

### 8.3.1 Direct Access to Patient Records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patients' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should be verifiable from source documents:

- all signed consent forms
- dates of assessments including dates specimens were taken and processed in the laboratory
- eligibility and baseline values for all participants
- all clinical endpoints
- all serious/severe adverse events
- routine patient clinical and laboratory data
- drug compliance
- dates drug dispensed and (if necessary) drugs returned
- pharmacy/clinic drug logs
- concomitant medication.

### 8.3.2 Confidentiality

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a trial identification number and this will be used on CRFs; patients will not be identified by their name. The investigator will keep securely a patient trial register showing identification numbers, surnames and date of birth. This unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used, in order to maintain confidentiality, following the principles of the UK DPA. All records will be kept in locked locations for 15 years after the end of the trial (see Section 12.1.3 Data Collection & Retention p62). Clinical information will not be released without written permission, except as necessary for monitoring, auditing and inspection purposes.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 METHOD OF RANDOMISATION

Randomisation will be stratified by clinical site. Randomisation lists will be computer-generated at MRC CTU at UCL by the Trial Statistician based on random permuted blocks with variable block size. The generated randomisation lists will be securely incorporated within the ARREST database provided by MRC CTU at UCL, and allocation will be concealed until the point of the next randomisation. A reliable manual back-up system will also be available. Randomisation will not take place until after informed consent has been given and the participant is ready to receive therapy. Authorised individuals (according to the Signature List and Delegation of Responsibilities Log) at each site can then carry out randomisation at https://macro.ctu.mrc.ac.uk/macro/

The study pharmacist in each NHS Trust will have access to a copy of the randomised allocations for each ARREST trial number for their site, in order to prescribe IV rifampicin if required (see section 5.2.3 Blinding Issues p30). Only the study pharmacists, the trial statisticians and Sharp Clinical Services (manufacturing placebo, packing placebo and active capsules) will have access to the randomisation codes.

## 9.2 OUTCOME MEASURES

The trial's primary outcome will be:

- death or microbiologically confirmed treatment failure or disease recurrence (bacteriological failure) up to 12 weeks from randomisation.

We have chosen this primary outcome measure as it is a severe event, and is thus highly unlikely to be influenced by unintended unmasking of treatment allocation (for example, through rifampicin discolouring urine) and, if significantly reduced by rifampicin, will provide an unequivocal stimulus to change practice. 12 weeks has become the standard duration of follow-up for studies of *S. aureus* bacteraemia, as few *S. aureus*-related events (either disease recurrence or death) occur after 12 weeks.

Microbiologically confirmed treatment failure will be defined as symptoms and signs of infection for longer than 14 days from randomisation with the isolation of same strain of *S. aureus* (confirmed by genotyping) from a sterile site (e.g. blood, joint fluid, pus from tissue). Disease recurrence will be defined as the isolation of the same strain of *S. aureus* from a sterile site after at least 7 days of apparent clinical improvement. The same strain will be defined as one with the same genotype by multi-locus sequence (37) and spa-typing (38).

The secondary outcome measures will be:

- all cause mortlity up to 14 days
- death or clinically defined treatment failure or disease recurrence by 12 weeks (clinical failure being assessed by an independent endpoint review committee blind to the treatment allocation)
- duration of bacteraemia (blood cultures will be taken on days 3 and 7 following randomisation)
- development of rifampicin resistant *S. aureus*
- grade 3/4 adverse events
- serious adverse events

- modification of any treatment (including concomitant medications) due to drug interactions.

Our current observational data from the proposed trial sites shows that 70% of deaths from *S. aureus* bacteraemia occur within the first 14 days after initiating treatment. In addition, 70% of these early deaths were attributed by the attending physicians to be directly related to the infection as opposed to 35% after 14 days. If our hypothesis is correct, and rifampicin improves survival through enhanced early bacterial killing then the first 14 days are when the greatest differences between groups are likely to occur in all-cause mortality. In addition, because standard therapy is given intravenously for at least 14 days this endpoint will almost always be assessed in hospital before discharge, reducing losses to follow-up.

Liver function tests will be performed twice (days 3 and 7) whilst on rifampicin/placebo and all significant drug interactions requiring modification of study and non-study medication will be documented. Rifampicin resistance may not be detectable until treatment fails or the disease recurs and *S. aureus* can be re-cultured from blood or another sterile site.

Other outcomes will be:

- compliance with blinded rifampicin/placebo
- healthcare-related costs of *S. aureus* bacteraemia
- EuroQol-5D questionnaire (EQ-5D)

Protection against bias is by the use of blinding, given potential issues with rifampicin discolouring urine/tears/sweat. Any patient lost to follow-up before 12 weeks without withdrawing consent will be traced for vital status. The primary and secondary clinical endpoints will be adjudicated by an independent endpoint committee blind to the treatment allocation, in order to minimise the impact of potential unblinding of some patients on the main results of the trial.

Cause of death, microbiological and clinical treatment failure/recurrence will be adjudicated by an Endpoint Review Committee, blinded to randomised allocations (see Section 15.5 - Endpoint Review Committee p69). The ERC will be asked to adjudicate a relationship to rifampicin without knowing whether or not the patient was actually taking rifampicin or placebo.

## 9.3 SAMPLE SIZE

Recruitment to the trial has been slower than anticipated. To facilitate successful completion of the trial and at the request of the trial funder, 14-day mortality has been moved from a co-praimry to a secondary endpoint. 12-week bacteriological failure/recurrence or death is therefore the sole primary endpoint with consequent decrease in sample size (due to increase in the two-sided alpha (Type I error) from 0.025 (two co-primary endpoints) to 0.05 (one primary endpoint)). The reason for choosing to keep the 12-week co-primary endpoint as primary is because of the duration of illness.

Sample size calculations and assumptions in the orginal protocol: Our current observational study data indicate 16% and 24% of all cases of *S. aureus* bacteraemia die by 14 days and 12 weeks respectively. Data from Oxford and the HPA (personal communications) suggest that a further 10% of patients have repeat isolation of *S. aureus* over the 12 weeks following initial bacteraemia. Assuming 80% power, two-sided alpha 0.025 (to adjust for multiple testing given 2 co-primary endpoints), and a 10% loss to follow-up by 12 weeks, we would need to randomise 920 patients to detect a 30% relative reduction in bacteriological failure/death from 35% to 25%, an absolute difference of 10% corresponding to an number needed to treat (NNT) of 10. The meta-analysis of RCT data (Figure 1) suggests adjunctive rifampicin reduced infection-attributable death by around

50% in all patients with serious *S. aureus* infections (relative risk 0.45, 95% CI 0.23 to 0.89), with a similar, albeit non-significant, effect in the sub-group with bacteraemia (relative risk 0.46, 95% CI 0.13-1.59). These findings strongly support a large effect size (40-50% relative reduction) in mortality. Assuming 80% power, two-sided alpha 0.025, and a lower 4% loss to follow-up by 14 days (as most patients will remain in hospital), we would need to randomise 940 patients to detect a 45% relative reduction in mortality from 16% to 9%, an absolute 7% difference and a NNT of 14. **The total sample size is therefore 940 patients.** This provides 68% and 57% power to detect smaller relative differences of 25% and 35% in bacteriological failure/death and death, respectively (other assumptions as above, alpha=0.025).

Sample size re-calculation in protocol version 5.0: With 12-week bacteriological failure/recurrence or death as the sole primary endpoint, the total sample size is now 770 patients (alpha=0.05, other assumptions as above).

## 9.4 INTERIM MONITORING & ANALYSES

A DMC Charter will be drawn up that describes the membership of the DMC, relationships with other committees, terms of reference, decision-making processes, and the approximate timing and frequency of interim analyses (with a description of stopping rules and/or guidelines). The DMC will meet within 6 months of the trial opening; although the DMC will meet at least once per year, the frequency of subsequent meetings will be determined by the DMC and could be more frequent if they deem necessary. The DMC can recommend premature closure or reporting of the trial, or that recruitment be discontinued or modified. Such recommendations would be made if, in the view of the DMC, there is proof beyond reasonable doubt that one of the allocated strategies is better than its comparator in terms of a difference of clinically significant magnitude in the primary outcome. The guiding statistical criteria for "proof beyond reasonable doubt" are Haybittle-Peto type rules based on the 99.9% confidence intervals of the relative hazards of all-cause mortality, and death or microbiologically confirmed treatment failure or disease recurrence, in each interim analysis. See Appendix I - Trial Steering Committee and Data Monitoring Committee Membership p80 for membership.

## 9.5 ANALYSIS PLAN (BRIEF)

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

Rifampicin is hypothesised to be superior to standard of care, and therefore the proposed analysis is intention to treat, including all randomised patients with all participants analysed according to the study group to which they were randomised regardless of subsequent treatment received. The primary endpoint (bacteriological failure/death through 12 weeks) will be compared using time-to-event methods (Kaplan-Meier plots and logrank tests, Cox proportional hazards regression), as will time to death to 14 days, and time to clinical treatment failure/bacteriological failure/death. Duration of bacteraemia will be compared using interval-censored time-to-event methods. For each endpoint, patients not completing follow-up and not known to have suffered an event will be censored at the date they were last known to be event-free in the primary analyses. For all-cause mortality (and death or microbiologically confirmed treatment failure or disease recurrence), sensitivity analyses will assume all such patients were alive (or alive and free from microbiologically confirmed treatment failure and disease recurrence) at 12 weeks (i.e. assuming that vital status tracing is robust and reliable). Primary analysis will not stratify for site, as there may be some sites

with no events who would therefore not contribute to treatment comparisons; secondary analysis will be conducted stratified. Primary analysis will include all randomised patients: secondary analysis will exclude those (expected <1%) who are subsequently identified as having rifampicin resistant *S. aureus* on susceptibility testing. The frequency of serious, grade 3 and 4, and drug-modifying adverse events will be tabulated by body systems and by randomised groups and the groups will be compared using Fisher's exact test.

Patients enrolled in the trial are likely to have heterogenous underlying conditions (e.g. cardiac, dialysis, cancer). However, precisely because the *S. aureus* bacteraemia will have been acquired in addition to any underlying reason, there is no a priori reason why rifampicin should be more or less effective in any comorbid subgroup, other than as a consequence of drug interactions with concomitant medications which will be assessed as a secondary endpoint. Planned subgroups analyses will therefore include time from initiation of antibiotics to initiation of randomised treatment, time from randomisation to initiation of randomised treatment, initial oral randomised treatment frequency (once vs twice daily), initial treatment with oral study drug only or regimen containg IV study drug, class of primary antibiotic treatment, other antibiotic adjuncts (e.g. gentamicin), MRSA/MSSA, IV catheter-associated infection/other, deep focus/no deep focus, endocarditis/no endocarditis, and age. An additional subgroup analysis will be conducted splitting participants into terciles of baseline CRP.

### 9.5.1 Cost Effectiveness Analysis

We will conduct a cost effectiveness analysis of therapy for *S. aureus* bacteraemia in the NHS. This analysis will be informed by the results of the trial. Due to the limited trial follow-up period and the possibility of existing treatment options other than those in the trial, we propose a framework based on decision analysis. Such an approach allows including findings from the trial in the context of the existing evidence on all treatments of interest and is the preferred approach for societal decision making in the UK.

Analyses will be built based on the requirements of the National Institute of Health and Excellence (41). The analysis will adopt a consistent perspective on costs (NHS/PSSRU), and and health effects will be expressed in terms of quality-adjusted life-years (QALYs). All economic analyses will be by intention-to-treat. A decision model will be developed with the aid of clinicians. By developing a model that adequately describes both the short and longer term consequences, we anticipate providing a full assessment of the impact on quality adjusted survival duration and costs of the alternative treatments. To inform such analyses further evidence will be sought in the published literature, but this will focus on reviews rather than on primary sources, i.e. reviews of reviews. Of special interest here is evidence on the clinical effectiveness of alternative treatments (including combinations of drugs). The evidence will be synthesised, if needed, for inclusion in the model.

The cost-effectiveness of alternative treatments will be represented using incremental cost effectiveness ratios (ICER) for each strategy evaluated. The decision to adopt one treatment strategy, rather than another, will be determined by comparing the ICERs to threshold values for the cost of an additional unit of benefit (NICE uses a threshold of £20,000 to £30,000 per QALY gained), using a full incremental analysis (41).

Uncertainty will be evaluated using probabilistic sensitivity analysis based on Monte Carlo simulation (42). Decision uncertainty will be characterised by an evaluation of the probability of each strategy being cost effective, for a range of threshold costs of an additional QALY. Cost effectiveness acceptability curves (CEACs) can be use to display such information in a plot (43, 44). We also aim to explore patient heterogeneity by performing subgroup analysis. Relevant subgroups for analysis will be defined from the ones used in the clinical effectiveness analysis.

# 10 PATIENT AND PUBLIC INVOLVEMENT

The ARREST trial has been developed with the Healthcare-associated Infection Service Users Research Forum (SURF: www.hcaisurf.org); in particular Jennifer Bostock who will represent SURF on the ARREST Trial Steering Committee (Appendix I - Trial Steering Committee and Data Monitoring Committee Membership, p80). Ms Bostock has advised on the inclusion of incapacitated adults and the application of the Mental Capacity Act, and the information provided to patients. SURF will also help disseminate the trial's results beyond the academic and healthcare professional community to other patient groups and the wider public.

# 11 ANCILLARY STUDIES

There are three ancillary studies to the main trial. Participants enrolled from specific trial centres will be approached for additional consent for the first PK/PD study (see below); all participants will be approached for additional consent for the second (host DNA/RNA). Patients/legal representatives who do not consent to participation in the trial will be offered the opportunity to complete a questionnaire exploring reasons for this; participants/legal representatives at one trial centre who did consent will be offered the opportunity to be interviewed by the ARREST patient and public representative to explore their experiences of trial participation.

## 11.1 A POPULATION PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) STUDY OF RIFAMPICIN, FLUCLOXACILLIN AND VANCOMYCIN FOR THE TREATMENT OF *S. AUREUS* BACTERAEMIA

The aim of the PK-PD substudy is to determine the pharmacological parameters of rifampicin which best predict treatment success and provide a rational basis from which optimal dose, frequency, and route of administration can be modelled statistically and/or explored in future studies. If the trial results are negative, these data will be able to identify whether this is because of issues with the dosing schedule or the susceptibility of the bacteria, or both. If results are positive, these data will identify whether greater benefits could be achieved, either overall or in some groups of patients (stratified medicine). Consent for this substudy will be sought separately to main trial consent. The design for the population PK/PD analysis of rifampicin will enrol patients from up to 6 of the trial sites (Guy's and St. Thomas', University College London Hospitals, Cambridge, Oxford, Brighton, and Liverpool) and will consist of both sparse and intensive subdesigns to optimise precision of the parameters at the most cost-effective sample size. Using literature estimates of PK parameters of rifampicin and unpublished data the proposed design was evaluated using the Population Fisher's Information Matrix method based on a one compartment model for the drug. This was implemented in PopDes 4.0 (Centre for Applied Pharmacokinetic Research, University of Manchester) using the D-optimality criterion and the hybrid simplex-simulated annealing algorithm to identify optimal designs. At least three occasions were specified as a means to enable estimation of inter-occasion variability and synchronise with the measurements in the PD component of the study.

| Subdesign | Number of patients | Number of samples | Sampling times (hours post daily dose of rifampicin)* |
|---|---|---|---|
| Intensive | 70 | 8 | Day 1; 0-1hrs, 2.5-3.5 hrs; Day 3 0.5-1.5 hrs, 1.5-2.5 hrs, 6-9 hrs, 10-12 hrs; Day 7 1.5-2.5 hrs and 6.5-8.5 hrs. |
| Sparse A (Oxford) | 110 | 3 | Day 1; 1-3 hrs, 6.5-8.5 hrs; Day 3; 10-12 hrs. |
| Sparse B (Brighton, Liverpool) | 110 | 3 | Day 1 10-12 hrs; Day 3 0-1 hrs and 2-4 hrs. |

* The sampling days can vary +/- 1 day (to avoid weekend sampling). For all samples, it is critical the precise date and time of sampling is recorded in the CRF. For further details please see the PK/PD laboratory manual.

The expected coefficient of variation (CV%s) of the fixed effect parameters of the one compartment model for rifampicin under these assumptions are estimated to be Ka 7.85% Cl 4.17% and Vd 3.99%

with precision for the area under the curve (AUC), believed to be the key PK-PD parameter in the same range.

These figures take into account the need for preservation of blinding. In total therefore it is anticipated that 1220 samples will be collected but that only 610 such samples from 145 participants randomised to rifampicin will be processed for the study drug. However, it will also be necessary to evaluate the primary antistaphylococcal drug concentrations in all of these samples since comparison of the PK/PD parameters between the control and rifampicin-treated groups will determine the relative contributions rifampicin makes to patients treated with flucloxacillin, vancomycin or teicoplanin. These investigations will be especially pertinent in those with MRSA bacteraemia as there is growing concern that MRSA with reduced susceptibility to glycopeptides is having a detrimental effect on outcome (45). Rifampicin may therefore have a greater impact on bacterial killing and clinical outcome in this sub-group.

The study will therefore also support PK modelling of the primary anti-staphylococcal drugs with which rifampicin is given (flucloxacillin or either of the glycopeptides vancomycin and teicoplanin). The current design will be refined using a joint optimisation algorithm for these agents based on appropriate structural models (two or three compartment intravenous infusion) resulting in modified sampling schemes matched to participants treated for MSSA and MRSA capable of producing precise estimates for both of the drugs concerned and with modest windows to accommodate logistical errors in sampling execution.

### 11.1.1 INTENSIVE SAMPLING SUBDESIGN

Only patients enrolled at Guy's and St. Thomas' Hospitals, University College London Hospitals, and Addenbrookes Hospital, Cambridge, will be eligible to enter the intensively sampled subset (other centres may join later if additional resources become available). PK samples will be collected over three distinct occasions on days 1,3 and 7 totalling eight samples in total. At each time point 3 ml ml of lithium heparin blood will be collected on ice and under protection from light, transported to the laboratory, centrifuged and stored at -70 $^{o}$C. Please see the PK/PD laboratory manual for further details.

We hypothesise that rifampicin exterts its beneficial effect on outcome by enhanced intracellular activity. Therefore it is important to determine the location and quantity of the bacteria within the blood (extra- or intra-cellular) and the relative kinetics of killing in the two treatment arms. Whole blood (8-10 ml) will therefore also be taken at the same time points and innoculated directly into blood culture bottles. In addition, 10 ml of lithium heparin blood will be taken from these patients if local resources and personnel allow (dependent on site PI) on days 0, 1, 2, 3, 5, 7, 10 and 14 of treatment. The blood will be fycol centrifuged to separate the blood into liquid and cellular compartments and each compartment cultured for *S. aureus*. Each compartment will be cultured and aliquots of cells frozen for later analysis.

It is vital to accurately determine the kinetics of bacterial killing in the blood and it is likely that there will be only very small numbers of culturable bacteria, especially at the later time-points. Therefore, it is important to take whole blood cultures in addition to the heparinised blood to maximise the sensitivity of these assays and the likelihood of detecting viable bacteria. Clotted blood (5ml) will also be taken at the same time-points as the heparinised blood for the measurement of CRP. CRP provides an additional objective assessment of response to treatment. Additional consent will be obtained to take these samples. The PK and PD models provided from this subset of patients will be tested and refined using the data aqcuired from the larger, sparsely sampled group.

### 11.1.2 SPARSELY SAMPLED SUBDESIGN

Patients enrolled at Brighton, Oxford and Liverpool will be eligible to enter this study subdesign3 ml of lithium heparin blood will be taken over three separate occasions to a total of 3 samples, with participants from Oxford following the Sparse A schedule and patients from Brighton and Liverpool following Sparse B schedule timepoints to ensure adequate coverage of the three occasions specified in the intensive subdesign. Please see the PK/PD laboratory manual for further details.

For all participants in the sparse PK substudy blood cultures will be taken at the times specified for all patients in the trial (days 0, 3 and 7), with an additional blood cultures taken on days 1 and 2.

### 11.1.3 BIOANALYSIS

The specimens will be batched and the assays performed after every patient in the batch has completed the trial. Aliquots of plasma will be frozen and stored locally before being shipped to Liverpool for analysis. The laboratory team performing the drug assays (in Liverpool) will only be given the treatment codes for each batch of patients. No information about rifampicin levels will be available outside the PK laboratory team before the end of the trial, although these results would be provided to the DMC. The laboratory team will perform the assays without knowledge of the patients' outcomes. Antibiotic concentrations (flucoloxacillin, rifampicin, vancomycin and teicoplanin) will be measured in plasma by high-performance liquid chromatography.. All assays will be performed in the GCLP-accredited bioanlytical facility using assay methods fully charactised and conforming with recognised international standards of external quality assessment and reporting.

Funding for this substudy will also be sought separately.

### 11.1.4 PK/PD MODELLING

Population PK modelling will be performed using NONMEM VII and R. Appropriate compartmental models will be fitted and model-derived estimates of exposure computed. These PK parameters will then be used as predictor variables in the PD models with the binary endpoints of bloodstream sterilisation by 3 days, microbiological failure, and death. Minimum inhibitory concentrations of flucloxacillin, vancomycin and rifampicin against the *S. aureus* cultured from each patient will also be considered as potential predictors in the models. Model checking will use graphical and simulation-based diagnostics. Thresholds and targets for optimal outcome will be identified using Classification and Regression Tree (CART) methods. The PK/PD analysis will not be started until the analysis of overall trial results is complete.

## 11.2 THE INFLUENCE OF HOST AND BACTERIAL GENETICS ON DISEASE SEVERITY AND OUTCOME FROM *S. AUREUS* BACTERAEMIA

Our aim is to identify host and bacterial genetic factors which influence disease severity (for example, the development of metastatic complications) and poor outcome from *S. aureus* bacteraemia. The well-characterised patients enrolled into the trial provide a unique opportunity to assess these factors and thereby provide important insights into disease pathogenesis. Consent will be sought to extract and store DNA and RNA from each patient for these investigations. Bacterial genetic variation will be assessed by multi-locus sequence and spa-typing and, when greater resolution is required, whole genome sequencing. A single nasal swab taken at baseline will allow us to compare colonising and invasive *S. aureus* strains. Host genetic determinants of infection phenotype will be investigated though candidate gene and whole genome association and expression studies (funding to be sought separately). These data will identify targets for future therapeutic strategies, and may also identify patients at greater or lesser risk of poor outcomes.

The host genetic specimens taken for this future sub-study will be stored locally, before being shipped to the King's College London Infectious Diseases biobank for archiving for 10 years from the end of the study. The bacteria will be archived in Oxford and Brighton. The custodian of all the specimens stored from the trial will be the Chair of the UKCIRG (currently Guy Thwaites). Future investigations using these specimens will be co-ordinated by the Chair of the UKCIRG, although none of the specimens will be used for any future investigations without the written permission of each centre's PI.

## 11.3 EXPERIENCES OF BEING APPROACHED FOR TRIAL PARTICIPATION, THE CONSENTING PROCESS AND TRIAL PARTICIPATION

### 11.3.1 PATIENTS/LEGAL REPRESENTATIVES WHO DO NOT CONSENT TO TRIAL RECRUITMENT

The overall objective of this substudy is to identify patient and legal representative barriers to recruitment. This will serve the following purposes:

1. To aid learning about why patients/legal representatives did not consent to being in this trial and whether there are any improvements that can be made to the information giving and/or the consent process which may encourage greater participation in a future similar study, or in the ongoing ARREST trial.

2. To give patients/ legal representatives choosing not to join the study a voice in order that researchers learn of any unintended barriers in the way in which information is given and/or consent taken when recruiting patients with serious illness.

At the time that they did not consent to the study, patients/legal representatives from all participating NHS Trusts would be given a short, completely anonymous, questionnaire (Appendix VII) with a stamped addressed envelope, which could be completed at any time in the future and posted directly to the MRC Clinical Trials Unit at UCL. Completing the questionnaire will be considered to indicate consent to do this, ie no additional consent will be sought. Healthcare professionals involved in consenting patients to ARREST and who were asked to act as legal representatives but did not consent for the patient to join the study will also be provided with a parallel questionnaire (Appendix VIII).

At the Guy's and St Thomas's centre, at the end of the questionnaire, participants/legal representatives would be offered the option of being interviewed by the ARREST patient and public involvement (PPI) advisor (who has experience in conducting interviews). If they would like to be interviewed, they would be asked to provide their name and contact details, and this would indicate consent for an interview. We would aim to get experiences from ~3 potential participants and ~3 legal representatives who were not healthcare professionals not providing consent to join the trial, but would continue up to 10 participants if new views and experiences were continuing to be expressed (that is, had not reached saturation). The interview guide would follow the questions in the questionnaire, seeking to obtain a more complete narrative of experiences around each aspect.

### 11.3.2 PARTICIPANTS/LEGAL REPRESENTATIVES WHO DO CONSENT TO TRIAL RECRUITMENT

The overall objective is to sample views on experiences of trial participation – what participants or their (personal) legal representatives liked, and what they did not like and think the trial could have done better. This information will serve the following purposes:

1. To gain valuable insight into the experience of participating in such a trial – the reasoning behind participation and the pros and cons of being involved.

2. To gain an understanding of the 'patient perspective' and how this might inform future trials to improve them, and potentially how the ongoing conduct of the ARREST trial could be improved.

3. To examine the process of consent and information giving at the time of consenting the patient, and whether there are any barriers which might be improved to aid recruitment in future.

4. To run as a parallel narrative alongside the feedback from clinicians and researchers involved in the study to explore differences, commonalities and pool suggestions for improvements for future studies.

This will be an interview study conducted at one centre, Guy's and St Thomas's NHS Trust. Since participants are typically very unwell when they join the study, the approach to each patient to discuss the interview study and seek additional consent for this will be made at a varying time after randomisation depending on clinical status. For most patients this would be 2-3 weeks from randomisation, when their clinical status has improved and discharge is being planned. However, it could be at any time up to their final 12 week ARREST follow-up visit. The research nurse provide an additional information sheet (Appendix IX), to ask if they would be willing to have a short (20-30 min) semi-structured interview about their experiences of trial participation with the ARREST PPI advisor (not a member of the trial team). If they agree and provide consent for this additional interview, then the ARREST PPI advisor will come to Guy's and St Thomas's NHS Trust to conduct the interview or will conduct the interview on the telephone at a time that is convenient for the participant. Both participants who gave consent originally or subsequently and legal representatives who gave consent for relative/friend participation would be approached.

We would aim to get experiences from ~3 participants and ~3 legal representatives who are not healthcare professionals, but would continue up to 10 participants if new views and experiences were continuing to be expressed (that is, had not reached saturation).

The interview would be semi-structured. The first set of questions would explore how participants/legal representatives viewed the process of recruitment,

1. Did you feel able to ask questions about the study?

2. Did you feel that your questions were answered satisfactorily?

3. Did you feel you had enough time to make up your mind?

4. What made it hard to agree to join the study? Were there things that the study team could have done differently to make the decision making process easier? (exploring the different barriers listed in the Questionnaire for non-consenting patients, Appendix VII)

The second set of questions would explore how participants/legal representatives viewed trial participation

1. Did you feel that you understood what was happening to you/your relative whilst you were in the study?

2. After you had joined, did you wish you hadn't?

3. What made it hard to continue to be in the study? Were there things that the study team could have done differently to make being in the study easier?

4. If a friend told you they had been asked to join a study, what kind of things would you tell them to find out about? Would you recommend they join (and why/why not)?

Any additional questions would directly relate to the objectives described above (ie why joined, what liked/disliked, what could have done better/differently, experience of consent, what would make them consider/not consider joining another trial in future).

#### 11.3.3 DISSEMINATION

The findings from these follow up questionnaires and interviews will be presented alongside the findings of the study at relevant conferences and also to patient groups and research networks to ensure that any lessons learned reach interested parties.

# 12 REGULATORY & ETHICAL ISSUES

All regulatory requirements (including safety reporting, see Section 7 - Safety Reporting p43 and below) will be met by the co-sponsors or their delegated authorities. We will follow the statutory requirements for consent as set out in the schedule 1 of the Medicines for Human Use (Clinical Trials) regulations, particularly as they relate to incapacitated adults, with legal representatives (LRs) definitions applied according to these regulations. Emergency recruitment, as defined in the regulations, will not be sought for the trial as the investigators have 96 hours from the start of active antibiotic treatment to enrol patients.

## 12.1 COMPLIANCE

The trial end is 12 weeks after the last patient is randomised (end of follow-up for the last randomised patient).

### 12.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the Declaration of Helsinki (2008).

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 (The Medicines for Human Use [Clinical Trials] Regulations 2004) and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

### 12.1.2 SITE COMPLIANCE

All sites will comply with the above. An agreement will be in place between the site and the MRC CTU at UCL, setting out respective roles and responsibilities (see Section 13 - Finance p67).

The site will inform the Trials Unit as soon as they are aware of a possible serious breach of compliance, so that the Trials Unit can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial

### 12.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 15 years after the end of the trial. During this period, all data should be accessible to the competent authorities and the co-sponsors with suitable notice. The data may be subject to an audit by the competent authorities. Electronic data will be kept for at least 20 years at the MRC CTU at UCL.

## 12.2 ETHICAL CONDUCT OF THE STUDY

Written, informed consent will be obtained from all patients, or their legal representatives (LRs) if they lack capacity, before enrolment by the site PI or an appropriately trained Consultant, Specialist Registrar, or Research Nurse (seniority band 6 or above). Permission for these individuals to consent

patients will be sought from the trial sponsors, relevant REC, and hosting NHS organisation. They will be documented on the trial's Delegation Log (with signatures). Patients (or their LRs) would be free to withdraw from the trial at any time, and this will be explicitly stated in patient information sheets.

### 12.2.1 ETHICAL CONSIDERATIONS

All patients will receive the best available, standard- of-care antibiotics, given as the 'backbone' of therapy against *S. aureus* bacteraemia. These antibitoics have no adverse interactions with rifampicin – but all require an IV line to already be inserted to receive them. Therefore, no participant would have a line inserted specifically for the purposes of the trial, and the main risks to trial patients are rifampicin-associated toxicity and rifampicin-induced changes in metabolism of other non-antibiotic medications. The majority of study assessments will be conducted whilst the patient is hospitalised, with just one additional outpatient follow-up visit (routinely undertaken in some sites aleady) and the amount of extra blood taken is modest.

Rifampicin is given to around 9 million people each year as the first-line, 6-month treatment of tuberculosis. It is well tolerated and there is extensive experience amongst all the trial centres investigators (infectious diseases physicians and microbiologists) of its safe use. Hepatitis is the most important side-effect of rifampicin: asymptomatic rises in liver transaminases occur in around 10% of patients taking rifampicin and requires no action other than careful monitoring. Significant rifampicin-induced hepatitis (transaminases >5x upper limit of normal (ULN) +/- symptoms) is rare (<1% of patients) and usually resolves with discontinuation of the drug. The liver function tests of patients will be monitored twice whilst taking the study drug (day 3 and day 10), which is more frequent than recommended by NICE when using rifampicin to treat tuberculosis (46). However, the trial patients are likely to be more acutely unwell than patients with tuberculosis and may require closer monitoring. Potentially fatal hepatic injury is extremely unlikely given the relatively short course of rifampicin, tight laboratory monitoring, and early withdrawal if the transaminases rise >5X the upper limit of normal likely due to rifampicin. The commonest side-effect of rifampicin is orange urine, but this effect is completely harmless. Rifampicin also colours tears orange (and can stain contact lenses).

Rifampicin induces the hepatic metabolism of many other drugs which can result in their sub-therapeutic concentrations. The recruiting infection specialists will be responsible for identifying clinically important interactions and ensuring appropriate action is taken to reduce the risks to patients; this may include judging patients receiving these medications as not eligible to join ARREST.

Against these risks, trial patients may benefit from receiving rifampicin by its ability to kill *S. aureus* more effectively, reduce the risk of treatment failure and improve their chances of surviving the infection. In addition, all patients will benefit from the careful observation and follow-up over 12 weeks from enrolment, which will allow infection complications (treatment failure, metastatic spread, recurrence) to be rapidly identified and managed.

The potential development and dissemination of rifampicin resistant organisms is the only risk the trial presents to society. Quantifying this risk from published studies is difficult, but the development of rifampicin resistance during treatment is an important trial endpoint.

The risks and benefits of participation will be communicated in two ways. First, all potential patients or their LRs will be given a patient information sheet clearly listing the risks and benefits of the trial. The information sheets have been developed in collaboration with the Healthcare Associated Infection Service Users Forum (SURF) (users group) to ensure they communicate the risks and benefits clearly and appropriately. Second, all potential patients (or their LRs) will be able to discuss

participation with their consulting infection specialist/research nurse who will be able to address questions not covered or arising from the patient information sheet.

The trial protocol will seek ethical approval to include incapacitated adults in the trial as we consider many of these adults will have the most severe infection and therefore represents the group that might stand most to gain from the enhanced anti-microbial activity of rifampicin. We anticipate around 10% of patients with *S. aureus* bacteraemia will be critically ill and incapacitated on intensive care. In this circumstance, the site PI, or another experienced and independent physician will follow the Mental Capacity Act (2005) to formally assess the capacity of the individual to make an informed decision to participate in the trial. The reason for incapacity must be directly related to the infection; consent will not be sought from those incapacitated for other reasons (e.g. due to dementia). Once incapacity has been confirmed written informed consent will be sought from either a personal (e.g. a relative) or a nominated LR (e.g. Consultant Intensivist caring for the patient, but not involved in the trial). If the subject regains capacity during treatment they will be informed of the consent given by their LR and their wishes respected concerning on-going participation. If they are happy to remain in the trial, the patient should complete a patient consent form at this time (Appendix III - Trial Consent forms p89). If they wish to withdraw from the trial, no further trial-related procedures will be performed, but data to this point would be used in analysis. Data from any patient who dies before regaining capacity (but whose LR has provided consent) will be included in analysis.

Patients' confidentiality will be maintained throughout the trial. Data submitted to MRC CTU at UCL and samples sent to central testing facilities will be identified only by the trial number and patient initials.

### 12.2.2 ETHICAL APPROVALS

Before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective patient will be submitted to a central ethics committee for approval. Any further amendments will be submitted and approved by the relevant ethics committee.

The rights of the patient to refuse to participate in the trial without giving a reason must be respected. After the patient has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. The reason for doing so, however, should be recorded; the patient will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the patient must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

## 12.3 COMPETENT AUTHORITY APPROVALS

This protocol will be submitted to the national competent authority (MHRA). This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK. The EUdraCT number for the trial is 2012-000344-10.

The progress of the trial and safety issues will be reported to the competent authority in accordance with local requirements and practices in a timely manner. Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with their requirements in a timely manner.

## 12.4 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required. A copy of the local R&D approval (or other relevant approval as above) and of the PIS and Consent Form (CF) on local headed paper should be forwarded to the MRC CTU at UCL before patients are entered in to the study.

# 13 INDEMNITY

University College London (UCL) holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, via the ARREST Trial Manager, who will pass the claim to the UCL's Insurers, via the UCL's office.

# 14 FINANCE

The trial is supported by grant funding from the National Institutes of Health Research (NIHR) Health Technology Assessment (HTA) Programme (10/104/25).

The trial will be coordinated by the MRC CTU at UCL. A written agreement with the NHS Trust or Board of each site principal investigator (PI) and the MRC CTU at UCL will set out the obligations of the parties to the agreement, their respective roles and responsibilities and cover arrangements for budgets and financial transfers and reporting. The study will also be registered through the NIHR portfolio system for adoption by the Comprehensive Local Research Network (CLRN).

# 15 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

## 15.1 TRIAL MANAGEMENT TEAMS

A Trial Management Team (TMT) will be formed to conduct the day-to-day management of the trial at the MRC CTU at UCL. This will include the Chief Investigator, Trial Statistician, Clinical Project Manager, Trial Manager and Data Manager, as required. The group will meet at least once per month, although may meet more or less often as required. The group will discuss issues related to the progress of the trial at the site and to ensure that the trial is running well.

## 15.2 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit (CTU), as required. The TMG will be responsible for the day-to-day running and management of the trial. It will meet approximately three times a year, at least one of which will be in-person. At these meetings, progress and challenges will be summarised and difficulties discussed. This group will be chaired by the Chief Investigator and all decisions regarding the overall running of the trial will be made in this forum with the exception of matters of fundamental importance to the viability of the trial or that require major changes to the protocol. These will be referred to the Trial Steering Committee (TSC). The full details can be found in the TMG Charter.

## 15.3 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter. See Appendix I - Trial Steering Committee and Data Monitoring Committee Membership p80 for membership.

## 15.4 DATA MONITORING COMMITTEE (DMC)

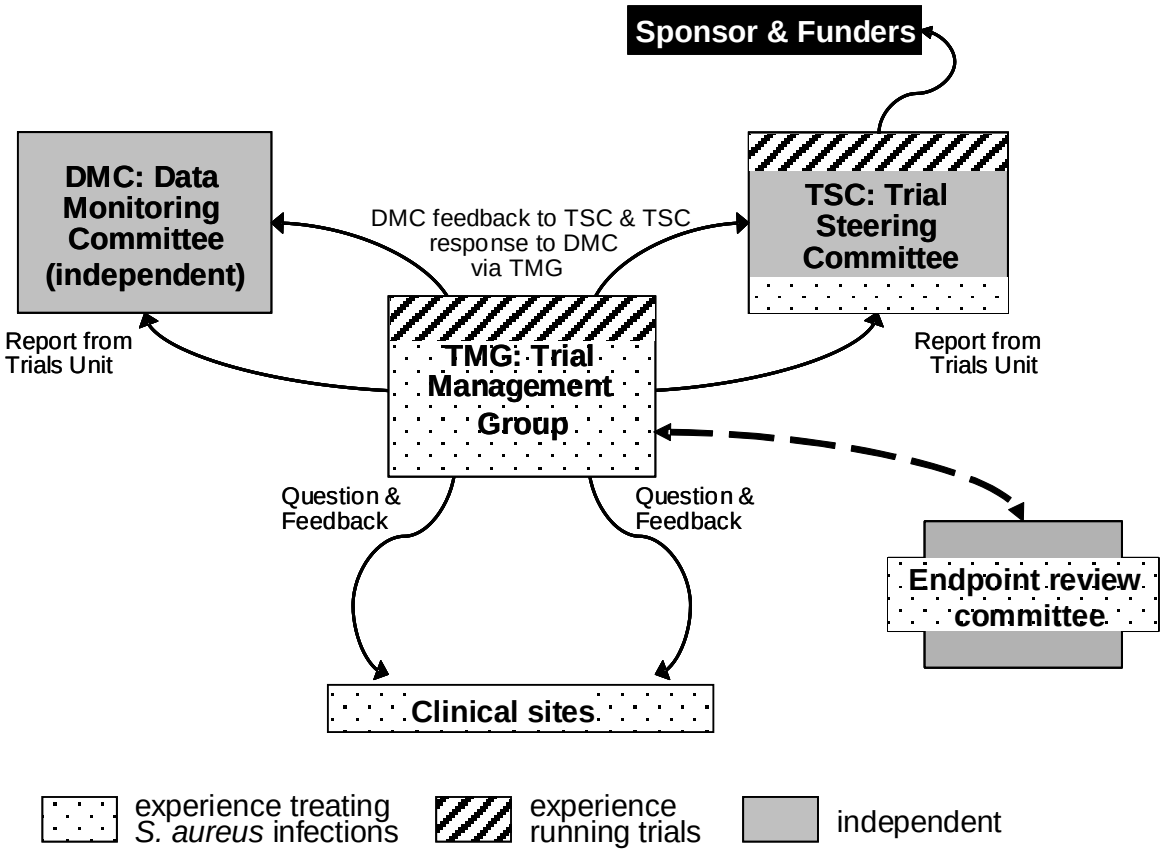
An independent Data Monitoring Committee (DMC) will be formed. The DMC will be the only group which sees the confidential, accumulating data for the trial separately by randomised group. Reports to the DMC will be produced by the MRC CTU at UCL statisticians. The DMC will review trial data on recruitment, safety, adherence to randomised strategies and efficacy, as well as consider findings from any other relevant studies. The DMC will meet within 6 months of the trial opening; the frequency of meetings will be dictated in the DMC charter. The DMC will consider data using the statistical analysis plan (see Section 9.5 - Analysis Plan (Brief) p53) and will advise the TSC. The DMC can recommend premature closure or reporting of the trial, or that recruitment be discontinued.

Further details of DMC functioning, and the procedures for interim analysis and monitoring are provided in the DMC Charter. See Appendix I - Trial Steering Committee and Data Monitoring Committee Membership p80 for membership.

### 15.5 ENDPOINT REVIEW COMMITTEE

An Endpoint Review Committee will be appointed whose remit will be to determine the validity of potential clinical endpoints in terms of meeting the criteria for microbiological and/or clinical treatment failure/recurrence, as defined by the protocol (Section 6.2 - Procedures for Assessing Efficacy p39). It will have an independent Chair and will include clinical representatives from the TMG as well as other independent clinicians. No member will review potential endpoints from their own site. Terms of reference for the Endpoint Review Committee will be drawn up.

**Figure 2. Trial Organogram**



## 16 PUBLICATION

(See Section 10 - Patient and public involvement p55 for plans for dissemination of results to participants and the broader community with HAI-SURF.)

The Chairman of the UKCIRG (currently Guy Thwaites) is the custodian of the data and specimens generated from the ARREST trial; ARREST trial data are not the property of individual participating investigators or health care facilities where the data were generated. However, the bacteria, the serum and the host DNA/RNA collected from a centre and stored within the ARREST trial according to the Trial Assessment Schedule page viii cannot be used for investigations not described in this protocol without the written permission of that centre's PI.

As the trial is planned be the largest ever performed in this serious infection, we anticipate there will be wide interest in the final trial results with publication in a major medical journal. UKCIRG members will promote dissemination of results widely across the NHS and ensure their maximal influence on clinical care. The results will also be disseminated to the public and patients through the Healthcare Associated Infection Service Users Forum (HAI-SURF).

However, it is anticipated that there may be opportunities for publication during the course of ARREST trial (not by randomised group). Publications include abstracts and oral/poster presentations for national and international meetings, as well as manuscripts for peer-reviewed journals. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the *Lancet* and from the publication policies used in other MRC clinical trials:

- All publications are to be approved by the TMG and TSC before submission for publication. Any publication arising before the end of the trial (not by randomised groups) will also be approved by the DMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. In particular, no analyses by randomised group of any outcome (primary, secondary or other) in either the main trial or associated substudies will be conducted or presented before the end of the trial, other than those for interim review by the DMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

- In line with MRC policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All conference presentations will be made available as soon as possible after the event via the ARREST website. All publications will acknowledge the trial's funding sources.

- For all publications, the TMG will nominate a chairperson or approve an individual's request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

- The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, substudy reports should include all

investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have a made a substantive academic or project management contribution to the work that is being presented. “Substantive” must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript and/or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

- The data derived from this clinical trial are considered the property of the Chairman of the UKCIRG (currently Guy Thwaites) held on behalf of the UKCIRG. The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of UKCIRG via the TMG and TSC (and the DMC before the end of the trial). This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the DMC before the end of the trial), they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC (and the DMC before the end of the trial). Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team.

- Outcome data by randomised group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The DMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

## 17 PROTOCOL AMENDMENTS

Version 1.01: Original version approved by the London-Westminster REC.

Version 1.02: Amended safety reporting text, as requested by the MHRA:
Page 3, SAE REPORTING: "within 1 working day" changed to "within 24 hours".
Page 44, 7.3 INVESTIGATOR RESPONSIBILITIES: "within 1 working day" changed to "within 24 hours".
Page 46, 7.3.1.E Notification: "within 1 working day" changed to "within 24 hours".

Version 2.0: Amended TSC Chair, as requested by the HTA:
Page i, Authorisation: Prof Jeremy Farrar changed to Dr Adrian Martineau.
Page 72, Appendix I: Dr Adrian Martineau named as Chair.

Major edits:
Page IX, 55, 56: Addition of University College London Hospitals to sites enrolling patients to intensive PK/PD study
Page IX, 38, 57: DNA ***and*** RNA stored for later genetic testing by storing 2.5mls of blood in PAXgene Blood RNA tube at day 0 (no change in total volume of blood taken at that time-point).
Page IX, 38, 56, 57: Clarification of sample storage and subsequent archiving.
Page 25, 32: Clarification that rifampicin susceptibility testing by disc test *or* Vitek is acceptable.
Page 76 , 77, Patient Information Sheets: Text changed to explain DNA and RNA will be stored for later genetic testing.

Minor edits:
Pages i and v: Added CTA and MREC reference numbers.
Page iii, MRC CTU Staff: Added Clinical Project Manager.
Page iv, Site Principal Investigators: Amended typographical errors in site names.
Page vi, duration: changed to patient 'recruited' rather than 'randomised' over 3 years
Page vii, Trial schema: 'consenting' changed to 'consented'
Page 14, Abbreviations: KCL and KHP CTO added
Page 23, 2.3 TRIAL CENTRES: Amended typographical errors in site names.
Page 27, 4.1 RANDOMISATION PRACTICALITIES: Amended CRF names. Amended text to clarify sample storage.
Page 30, TREATMENT SCHEDULE: clarified that those ≥ 60kg will receive 900mg rifampicin
Page 31, 5.3.1 DISPENSING: Amended text, "will be prescribed by the local pharmacist" changed to "will be dispensed by the local pharmacist".
Page 44, 7.2.1 PREGNANCY: Amended typographical error, "rifampicin in safe" changed to "rifampicin is safe".
Page 48, 8.1 RISK ASSESSMENT: Quality Management Committee changed to Research Governance Committee.
Page 58 and 63, Site compliance and Finance: agreement between site, KCL and MRC.
Page 81, 83, Appendix III: Version and date of patient information sheets and consent forms changed to Version 2.0, 23 August 2012. Reformatted optional consent boxes.
Page 85, Appendix IV: Added MREC reference number.

Version 3.0: Reasons for substantial amendment: (i) Remove King's College London (KCL) as Co-Sponsor, and (ii) Add four new trial sites:
Page i: Remove KCL logo
Pages ii and vii, Sponsor: Remove King's College London
Pages iv and v, Site Principal Investigators: Drs Sutton, Guleri, Minton and Munthali
Page 24, 2.3 Trial Centres: Southampton, Blackpool, Leeds and Coventry.
Page 63, INDEMNITY: Remove King's College London
Page 66, 15.6: Remove paragraph "Role of Study Sponsor"

Major edits to Intensive and Sparse PK/PD Substudy information:
Pages ix-xi, Trial Assessment Schedule (h), (i), (k): Changed timepoint of PK/PD lithium heparin blood collections from Day 0 to Day 1. Clarified total volume of blood to be collected. Added reference to PK/PD Laboratory Manual.
Page x, (j): Clarified procedure for Intensive PK/PD component studies.
Pages 56-58, 11.1-11.1.2: Updated sampling timepoints and procedures.
Page 81, Appendix II, Intensive substudy: Updated sampling timepoints.
Page 82, Appendix II, Sparse substudy: Updated sampling timepoints.

Major edits to bacterial genetic substudy information:
Pages ix and x, Trial Assessment Schedule (g): single nasal bacterial swab added at baseline.
Page 58, 11.2: Nasal swab added to study details. Clarification that bacteria will be archived in Oxford and Brighton.
Page 77, Appendix II, What will happen if I take part?, point 1: Updated to include baseline nasal swab.

Minor edits:
Page iii: Updated Randomisation summary and SAE reporting summary.
Page iii, MRC CTU Staff: Added Trial Statistician Alex Szubert.
Page iv, Chief Investigator: Updated CI address and email address
Page v, Site Principal Investigators: Updated Sheffield PI to Dr Julia Greig.
Page x, (h): Amended typographical errors "University of Liverpool" and "Davies".
Page 23, 2.2: Amended pack name and document name.
Pages 26, 3.4: "Trial register" changed to "Screening & Randomisation Register"
Page 28, 4 Randomisation: Added text to clarify randomisation via ARREST database.
Pages 30, 32, 35 and 51, 5.1, 5.2.2, 5.2.3, 5.3.1, 5.7, 9.1: Updated name of Clinical Trials Supplier to Sharp Clinical Services (formerly Bilcare GCS).
Page 31, 5.2.3 Blinding Issues, second paragraph, last sentence: Added text to clarify that infusion volumes used in the ITU may be altered in accordance with local standard practices and the product's SPC.
Page 31, 5.3 Treatment Schedule, third paragraph: Changed "intended" to "initial"
Page 32, 5.3.1 Dispensing, second paragraph, last sentence: Added text to clarify that temperature monitoring of treatment packs is not required after dispensing.
Page 32, 5.3.1 Dispensing, fourth paragraph: Changed "Dispensing Log" to "Accountability Log", and added "temperature monitoring".
Page 34, 5.5.2 Unblinding by the MRC CTU: Updated Trial Manager contact number.
Page 38, 6 Assessments & Follow-up, second paragraph: Added text to clarify that the final follow-up visit may take place over the phone.
Page 41, 6.6 Early Stopping of Follow-up, first paragraph: Amended CRF name.
Page 47, 7.3.2 Notification Procedure, points 1, 2 and 3: Updated text to clarify notification practicalities using the ARREST database.
Page 49, 8.2 Central Monitoring: Amended typographical error "Case Report Forms".

Page 51, 9.1 Method of Randomisation: Changed “website randomisation service” to “the ARREST database”. Updated name of Delegation Log.
Page 52, 9.2 Outcome Measures, last paragraph: Added “clinical”.
Page 53, 9.4 Interim Monitoring & Analyses, fifth sentence: Update text to clarify Haybittle-Peto rules in the context of this trial.
Page 53, 9.5 Analysis Plan (Brief), second paragraph: Added more detailed text regarding analysis of endpoints.
Page 54, 9.5 Analysis Plan (Brief), third paragraph: Changed “intended” to “initial”
Page 65, 15.1-15.2: Added “as required” to clarify TMT and TMG membership.
Page 77, Appendix II, What will happen if I take part?, point 3, second paragraph, second sentence: Amended error in text by removing day 7 timepoint.
Page 79, Appendix II, Storing samples: Added more detailed name of storage facility
Pages 84 and 86, Appendix III: Updated protocol version number and date.
Corrected typographical errors in Legal Representative consent form.

Version 4.0: Reasons for substantial amendment: addition of substudy – Experiences of being approached for trial participation, the consenting process and trial participation.

Major edits: addition of new substudy:
Page 56: Section 11 Text amended to include participation and consenting substudy and number of ancillary studies changed from two to three.
Page 59-61: Section 11.3 New section and text added to give details of the participation and consenting substudy
Page 95: Appendix VII Questionnare for non-consenting patients and legal representatives who are not healthcare professionals added
Page 98: Appendix VIII Questionnaire for non-consenting healthcare professionals added
Page 100: Appendix IX Information sheet for consenting patients or legal representatives added

Minor edits:
Throughout document: Change of name of coordinating site from Medical Research Council Clinical Trials Unit (MRC CTU) to Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL)
Throughout document: change of email address for coordinating centre from arrest@ctu.mrc.ac.uk to mrcctu.arrest@ucl.ac.uk
Page ii: Infections theme corrected to ARREST trial team.
Page iii: Coordinating site generic phone number removed
Page iii and iv: MRC CTU at UCL staff titles, names, email addresses and phone numbers updated
Page iv: Site Principal Investigators table removed
Page v: Protocol version and date updated
Page vi: trial manager name updated; Project lead title amended
Page vii: Amended Trials Schema error – day 10 added to follow up visits
Page viii: Added text to Trial Assessment Schedule footnote to clarify that if a patient is discharged before day 14 but is attending outpatient appointments then blood samples should be collected if possible.
Page 16: MRC CTU amended to MRC CTU at UCL; PEG and UCL added to Abbreviations table
Page 24: Section 2.3 Trial Centres removed
Page 25: Section 3.1 Added text to clarify that stat doses should be excluded from the 96 hour active antibiotic therapy in inclusion criteria

Page 31: Section 5.3 Added text to clarify that it is not permissable for IMP capsules to be opened and administered via PEG
Page 36: Section 5.8 Added text to clarify that if a patient receives additional doses of IMP for more than 24 hours i.e. 15 days of trial treatment then this must be reported as a protocol deviation
Page 39: Section 6.1 Added text to clarify that if a patient is discharged before day 14 but is attending outpatient appointments then blood samples should be collected if possible.
Page 44: Section 7.1.2 Moved bulletpoints describing adverse events that should be reported to Section 7.1 page 44 in order to prevent confusion. Added text to clarify that disease related events that are not fatal are exempt from being reported as SAEs
Page 49: Amended text to clarify that site initiation visits may occur either as a site visit or by WebEx teleconference
Page 66: Section 13 MRC Indemity text removed, UCL insurance text added
Page 79: Appendix I Professor Jeremy Farrar removed from TSC membership, Dr Achim Kaasch added; Trial statistician title amended
Page 80-86: Appendix II Friend/relative amended to friend/relative/patient to clarify that a doctor primarily responsible for a patient's medical treament may also act as a legal representative.
Page 87: Appendix II What is a Legal representative information sheet. Text added to clarify that a doctor primarily responsible for a patient's medical treatment may also act as a legal representative.
Page 88: Appendix III Trial participant Consent form.Updated protocol and version number. "Doctor's signature" changed to "Signature of person delegated to take consent" since some Trusts allow nurses to take consent
Page 90: Appendix III Legal Representative consent form. Updated protocol and version number. Friend/relative amended to friend/relative/patient to clarify that a doctor primarily responsible for a patient's medical treament may also act as a legal representative. "Doctor's signature" changed to "Signature of person delegated to take consent" since some Trusts allow nurses to take consent. Box for participant's name added.

Version 4.1: Minor edits requested by REC.
Page 92: Appendix IV GP letter amended to clarify that consent may have been granted by a legal representative. Version number and date of GP letter updated.
Protocol version number and date updated throughout protocol

Version 5.0: Reason for substantial amendment: Sample size reduced and co-primary endpoint (all cause mortality up to 14 days) reassigned as a secondary endpoint at the request of the funder

Major edits: sample size reduced and co-primary endpoint (all cause mortality up to 14 days) reassigned as a secondary endpoint
Page v Summary of trial: "All cause mortality up to 14 days from randomisation" removed as a primary endpoint, added as a secondary outcome measure.
Page vi Summary of Trial: number of patients to be studied changed from "940" to "770"
Page viii Trial schema updated to reflect change in sample size and endpoints
Section 1.5 Hypothesis and Objectives: "both all cause mortality up to 14 days from randomisation, and " removed as a primary objective, "evaluating the impact of

rifampicin on all cause mortality up to 14 days from randomisation" added as a secondary objective.
Section 3.3 Number of patients: number of patients to be studied changed from "940 patients (470 in each treatment arm)" to "770 patients (385 in each treatment arm)"; "enrolled over a target of 3 years" changed to "enrolled over a target of 3.5 years"
Section 6.2 Procedures for assessing efficacy: "All cause mortality up to 14 days from randomisation" removed as a primary endpoint, added as a secondary outcome measure.
Section 9.2 Outcome measures: "All cause mortality up to 14 days from randomisation" removed as a primary endpoint, added as a secondary outcome measure. Text modified to clarify.
Section 9.3 Sample size: updated to reflect sample size change from 940 to 770.
Section 9.5 Analysis Plan (Brief): All cause mortality up to 14 days from randomisation" removed as a primary endpoint.

Minor edits:
Page vi Summary of Trial: "3)experiences of being approached for trial participation, the consenting process and trial participation" added to Ancillary/substudies section (omitted in error in version 4.1 of protocol)
Section 5.3.1: "The ward nurse" Changed to "the ward or ARREST research nurse" to clarify that the ARREST nurse may take the prescription form to the pharmacy.
Section 5.3.2 Unblinding by MRC CTU at UCL: trial manager phone number corrected
Section 9.4 Interim monitoring analyses: Changed from "the DMC will in general meet" to "the DMC will meet at least once ber year" for clarification
Appendix VII Substudy questionnare: 'Relative/spouse', 'relative' 'friend/relative' have been corrected to 'relative/friend' for consistency.

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# APPENDIX I - TRIAL STEERING COMMITTEE AND DATA MONITORING COMMITTEE MEMBERSHIP

**Trial Steering Committee**

**Independent members**

| | |
|---|---|
| Dr Adrian Martineau | Chair; Clinical trialist |
| Dr Achim Kaasch | Infectious disease researcher, Clinical trialist |
| Dr Geoff Scott | Consultant Microbiologist |
| Ms Jennifer Bostock | Patient representative from the Service Users Research Forum |

**Non-independent members**

| | |
|---|---|
| Professor Guy Thwaites | Chief Investigator |
| Professor Sarah Walker | Trial Statistician |
| Dr Gavin Barlow | Clinician representing the ARREST TMG |
| Dr Susan Hopkins | Clinician representing the ARREST TMG |

**Data Monitoring Committee**

**Independent members**

| | |
|---|---|
| Prof David Lalloo | Chair; infectious diseases specialist with extensive experience of both conducting trials and Chairing DMCs. |
| Prof Mark Wilcox | Consultant microbiologist |
| Prof Doug Altman | Senior Statistician |

## APPENDIX II - TEMPLATE PATIENT INFORMATION SHEETS

**[Each NHS Trust to use its own Patient Information Sheet and Informed Consent according to local requirements on local headed paper]**

**The ARREST study (Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia)**

**Information for ALL Patients**
**(note: same patient information for legal representatives, with reference to "your relative/friend/patient" rather than "you". Legal representative to also be given the "What is a legal representative" sheet following this Patient Information Sheet)**

### Introduction

We are inviting you to take part in a research study called ARREST, which is being carried out in a number of NHS hospitals. The study is being funded by the National Institute of Health Research.

Before you decide if you want to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read this information sheet carefully or ask someone to read it to you. Please discuss it with others if you wish. We will give you a copy to keep. Please ask the nurses or doctors if there is anything that is not clear or if you would like more information. **Joining the ARREST study is entirely voluntary.** Please take time to decide whether or not you wish to take part.

You may decide that you do not wish to take part now or you may wish to take part now but then decide later to withdraw from the study. Your decisions will not influence the care you receive now or in future. We hope that if you decide to join the study but withdraw later, you would give a reason for your decision, but you do not have to do this if you do not want to.

### What is our reason for doing the ARREST study?

*Staphylococcus aureus* (or *S. aureus*) is a bug which can cause serious infections, including infections of the blood. Doctors use an antibiotic to cure *S. aureus* but sometimes the infection comes back and sometimes the antibiotic does not succeed.

We want to find out whether or not giving an extra antibiotic, called rifampicin, in addition to the standard antibiotic, will help sick people with *S. aureus* blood infections. We want to know if rifampicin can cure more people, possibly faster, or whether it makes no difference to how well people do. We also want to know if it gives more side-effects and/or encourages the bug to become resistant.

At the moment we do not know whether taking rifampicin as an extra antibiotic helps people with *S. aureus* blood infections and this is the reason we are doing the study.

### Why have I been asked if I would like to take part in the ARREST study?

You have been asked because your doctor thinks you have a blood infection with *S. aureus*. The doctor may already have started standard antibiotic treatment for this infection.

**What treatments will I be given?**

In the ARREST study we will give you the same standard antibiotic that you would receive if you decide not to join the study. In the ARREST study we will also give you EITHER rifampicin OR a "placebo" for a two-week period. A placebo is a dummy treatment, such as a pill, which looks like the real treatment (rifampicin) but it contains no active ingredient. It is a tool to help research.

This means that in addition to the standard antibiotic that you will get whether or not you join this study, in ARREST you will have an equal chance of getting rifampicin for 2 weeks or getting a placebo that looks like rifampicin for 2 weeks. In this way we create two groups of patients to study, and whether you get extra rifampicin or extra placebo will be chosen by chance by a computer.

Allocating additional rifampicin or placebo by chance is called randomisation, and means that the two groups of people getting each treatment should be very similar. This means that any differences in the two groups are probably because of the effects of the treatment we are studying, and not because doctors have treated one group of patients differently. Neither you nor your doctor will know which treatment group you are in because all the treatments will look the same (although if your doctor needs to find out he/she can do so).

**What will happen if I take part?**

If you are interested in taking part in the ARREST study, we will ask you to sign a consent form. After this the following will happen:

(1) The study doctor will examine you thoroughly and record details of your medical history, the current infection and the medications you are taking. He/she will take a sample of blood (25ml which is about 5 teaspoons in total) to culture the bacteria and to check the numbers of white cells in the blood, how your liver and kidneys are doing, and the amount of inflammation the infection is causing. We will also swab the inside of your nose to see whether the bacteria in your blood are also living (harmlessly) up your nose.

(2) A computer will decide which treatment group (rifampicin or placebo) you are in. The doctor and/or nurses will give you the drugs either through a drip or as tablets, and tell you all about the medicines and how to take them. If you need to get the drugs through a drip, we will use one that is already in place – no one will have a drip put into them just because they are in the study.

(3) After starting the ARREST study treatment, a study nurse will visit you 3, 7, 10, and 14 days later. This will then happen every week until you are discharged from hospital.

We will take a sample of your blood (10ml or 2 teaspoons) on day 3 and day 7 to see if the bacteria have been killed. We will also take an extra 10ml (about 2 teaspoons) of blood on day 3, 10 and 14 to check for any side effects and record the amount of inflammation the infection is causing. Some of these tests will be done even if you decide not to join the study, as part of routine care.

Some of the blood collected from you will be stored for tests that will be done later, such as tests to find out exactly how well your immune system was fighting the infection.

(4) We would like you to come back to clinic 12 weeks after joining the study for a check up visit to make sure everything is okay. If you are re-admitted to hospital for any reason before this 12 week visit, the study nurse will also come to see you in hospital to see how you are doing.

If you are unable to attend this 12 week visit, we will contact you or your GP by phone to find out how you are.

(5) After 12 weeks, there will be no more study visits. However, we would like to ask you if we can continue to see how you are doing by checking your routine medical records. This would be done for all patients when the last patient recruited to the study finishes their 12 week follow-up, and again 5 years after this.

**What are the possible risks of taking part?**

Like all medicines Rifampicin can have unwanted side-effects, which are sometimes serious. Serious side-effects with rifampicin happen in fewer than 1 in 100 people.

The most important side-effect of rifampicin is that is can cause inflammation of the liver. This can cause vomiting and abdominal pain. We will do regular blood tests to watch for this side-effect whilst you are in the study. If you experience symptoms tell your a nurse or doctor straightaway. It may be necessary to stop the study drug after which the problem usually goes away.

The other common side-effect of rifampicin is that it can turn your urine, tears and your sweat an orange colour. This is completely harmless and goes away completely when you stop taking the drug. It can stain permanent contact lenses, so you should remove these whilst you are on the study.

Finally, rifampicin increases the way your body breaks down some drugs. This can mean that these drugs become less effective. For example, rifampicin can stop the oral contraceptive pill working. Please let your doctor know all the medications you take before starting the study so that she/he can ensure rifampicin will not effect them.

As you will not know which group of patients you are in, you will not know if rifampicin is part of your treatment. This is why it is important that you should report any symptoms to your nurse. If you do not have symptoms, you may still be in the group receiving rifampicin, as many patients have no side-effects from the drug at all.

**What are the possible benefits of taking part?**

Taking rifampicin may help you fight *S. aureus* blood infection better. Whether you get rifampicin or a placebo, we will monitor you very carefully throughout your treatment and detect early any complications of the infection or side-effects of the drugs. Entering this study may not directly help you, but the information we get from the ARREST study should help patients like you in the future.

**How long will the study continue?**

You will be followed up in the study for 12 weeks (about 3 months). After this, we would like to check you are doing okay by contacting your doctor and looking at your medical notes when the study finishes and five years later.

**What happens to the information collected in the ARREST study?**

ARREST study nurses and doctors will collect information whenever they see you. This information will be stored in a computer and an independent committee, called the Data Monitoring Committee, will look at it regularly during the study to make sure it is safe for the study to continue. Information from the ARREST study will be analysed when it finishes and the results will be presented and published in the hope of improving the future care of adults with *S. aureus* blood infections.

**What about protecting my confidentiality?**

Information about you will be kept confidential and will not be made available to anyone who is not connected with the ARREST study. Your medical notes and study information will be available to study staff and may also be seen by other independent people authorised to ensure that the ARREST study is being properly carried out, for example staff from the UK Medicines and Healthcare products Regulatory Agency (MHRA). Strict confidentiality will be maintained at all times. Your name will never be used for study information or for stored blood samples; these will be identified only by a study number, date of birth and initials. There will be one list which links this study number to your name, and this list will be safely kept private in a locked cabinet by your doctor.

**What else do I need to know?**

Arrangements have been made for compensation if you come to any harm because of the study. If something does go wrong and you are harmed during the research and this is the result of negligence, then you may have grounds for a legal action for compensation against the NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. The trial sponsor will also consider making an ex-gratia payment in the event of non-negligent harm relating to taking part in this study.

**Storing samples**

Blood samples that are collected during the study will be used for immediate analysis, and some samples will be stored for future work that is connected to this study. New tests are being developed all the time, so we are asking if you would agree for your blood samples to be used in the future for any tests that are relevant to this type of infection, either during the ARREST study or after it ends. You will not be given results from these tests. These tests would be decided by a group of infectious diseases experts and any samples will never be identified by your name. These samples will be stored securely in the King's College London (KCL) Infectious Diseases biobank for 10 years from the end of the study.

**Leaving the study**

You may withdraw from the study at any time, but if you do it would help us if you are able to tell us the reason for this. However you do not need to tell us if you do not want to.

**Telling your GP**

We will also tell your GP that you are taking part in this study. When the study is finished in up to 3 years time we will write to your GP and let them know whether you received rifampicin or placebo in the study so that they can also tell you, and we will also tell them results of the study so that they can tell you.

**Genetic testing (optional)**

We would also like to ask your permission to use some of the stored blood for genetic testing. You do not have to agree to genetic testing to join the ARREST study, i.e. it is optional.

A genetic test is one carried out on DNA and RNA from a blood sample. DNA and RNA are the "letters" which make up the instructions which the body uses to do things. The DNA/RNA in your genes determines your physical characteristics, everything from your height, to your risk factors for disease, to how your body responds to different medicines. We inherit genes (genetic material) from our parents and the unique combination of the genes we have controls many body functions.

There are certain genes that influence how a person's immune system responds to infections like *S. aureus* and to medicines like rifampicin. There are other genetic factors that may also play an important role, but these are not yet known. The tests to identify any such genes would be done on

samples of blood that have already been taken for the study and involve extracting your DNA and RNA, or unique set of genes. Being able to match up the results of genetic tests with how you fight the *S. aureus* infection would be very valuable in working out how to treat people better in future.

If you agree, we will extract DNA and RNA at a future date from one of the stored ARREST blood samples. Because little is known about the significance of any findings from stored DNA/RNA, and because these tests will be performed at some date in the future, which is not yet determined, you will not be given results from findings related to this genetic testing. However, you can be assured that any genetic findings that the study shows may affect treatment will be made widely available to doctors and nurses working in the NHS, because the purpose of this research is to improve treatment for patients.

**How can I join the ARREST study?**

After you have read this information sheet, we will ask you to give consent to be seen by the doctor and to give a blood sample.

If you would like more information or have any questions about the ARREST study please ask the doctors, nurses or counsellors. If you still need more information, please call:

**Insert names and telephone numbers as appropriate:**

Name:

Telephone Number: …….

If you decide to join the ARREST study and have any concerns about any aspect of the ARREST study in the future, please also contact ..... on the telephone number above. If you remain unhappy and wish to complain formally, you can do this following the standard NHS Complaints Procedure (details can be obtained from ..... on telephone number ..... as above).

**Additional Information for Patients in the INTENSIVE Pharmacokinetic/Dynamic study (note: same patient information for legal representatives, with reference to "your relative/friend/patient" rather than "you". Legal representative to also be given the "What is a legal representative" sheet following this Patient Information Sheet)**

**Why am I being given extra information?**

In some patients taking part in the ARREST study we want to examine how rifampicin and the other antibiotics used to kill the *S. aureus* bug work in more detail. Rifampicin may help people with *S. aureus* blood infection by killing the bacteria faster. To determine whether this is true we would like to measure the levels antibiotics in your blood over the time you are on treatment. We need to study those given placebo and those given rifampicin in order to assess how rifampicin contributes to the activity of the other antibiotics. We will not know which treatment you are on when we take the blood, but those in the laboratory responsible for measuring the levels will be told. We would also like to see how the bacteria are killed in the blood and how your body reacts to the infection by measuring the amount of inflammation in your blood.

If you agree to participate in this optional part of the ARREST study, we would like to take a few extra tests to the ones we described in the main trial information sheet. These will help us determine how quickly the bacteria are being killed and how that relates to the antibiotic we are giving you. The details of the extra tests are as follows:

On days 1, 3 and 7 we will take a total of 8 blood samples from you: 2 on day 1, and 4 on day 3 and 2 on day 7. These are to measure the levels of antibiotics in your blood.

On days 0, 1, 2, 3, 5, 7, 10 and 14 of the study we would like to take around 8 teaspoons of blood from you. This is to determine how quickly the bacteria are being killed and whether any surviving bacteria are hiding within the cells of your blood. We will also store some of your blood white cells (the cells that help fight infection) for future tests. These tests will help us understand how *S. aureus* makes people ill and how the body responds to the infection.

**Additional Information for Patients in the SPARSE Pharmacokinetic/Dynamic study (note: same patient information for legal representatives, with reference to "your relative/friend/patient" rather than "you". Legal representative to also be given the "What is a legal representative" sheet following this Patient Information Sheet)**

**Why am I being given extra information?**

In some patients taking part in the ARREST study we want to examine how rifampicin works in more detail. Rifampicin may help people with *S. aureus* blood infection by killing the bacteria faster. To determine whether this is true we would like to measure the levels of rifampicin and other antibiotics in your blood over the time you are on treatment. We would also like to see how the bacteria are killed in the blood and how your body reacts to the infection by measuring the amount of inflammation in your blood.

If you agree to participate in this part of the ARREST study we would like to take a few extra tests to the ones we described in the main trial information sheet. These are as follows:

On days 0 and 3, we will take a total of 3 blood samples from you: 2 on day 0, and 1 on day 3 or 1 on day 0, and 2 on day 3. These are to measure the levels of antibiotics in your blood.

On days 0, 1, 2, 3 and 7 of the study we would like to take around 2 teaspoons of blood from you for culture. This is to determine how quickly the bacteria are being killed and whether any surviving bacteria are hiding within the cells of your blood.

**The ARREST (Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia) trial**

**What is a legal representative?**

This additional information sheet covers the role of a personal legal representative.

**What is a legal representative?**

Where a potential study participant is unable to decide for him or herself whether to participate in the research someone who knows them well is asked to make a decision for them. The person making the decision is known as a "legal representative".

**Why have I been asked to be a legal representative?**

The medical and nursing team caring for your family member or friend have suggested that you know them well and your family member or friend would trust you to make important decisions about their well being and what they would want to happen (their presumed will or intentions). Your family member or friend is very sick with a blood infection caused by a bug called *Staphylococcus aureus* and there is a research study which they could join and which might, or might not, benefit them. We are asking you because, due to the infection, they are not well enough to decide for themselves. If you are the doctor who is primarily responsible for the patient's medical treatment then you may have been asked to act as a legal representative if all efforts have been made to contact family members and it has not been possible to identify one.

**Do I have to be a legal representative?**

No, being a legal representative is completely optional, and if you choose not to be a legal representative this will not affect the care of your family member/ friend/patient in anyway. If you do not wish to be a legal representative, we would welcome any suggestions you have about whether there is anyone else who might be a good person to ask to be a legal representative.

**What does a legal representative need to do?**

We would like to explain the research study to you, and provide you with the same information we would offer to any potential participant. We would then like you to consider whether your family member/friend/patient would want to take part. That is, what the past and present feelings and wishes of your family member/friend/patient would have been about taking part in the study. We are not asking for your own personal views on the study, but to consider the interests and views of the person potentially taking part in it. If you think that your family member/friend/patient would be content to take part we would like to include them in the study and to keep a record of your agreement that they should join by asking you to sign a Legal Representative Consent Form.

If you have any questions please feel free to ask the member of the research team you provided you with this sheet, or to contact the team on the number below. Thank you.

**Insert names and telephone numbers as appropriate:**

Name:

Telephone Number: …….

## APPENDIX III - TRIAL CONSENT FORMS

# - Trial Participant -

(To be presented on local-headed paper: same version for legal representatives except “me “ rather than my friend/relative/patient” ”)
Version 4.1 Date 14 August 2014

# ARREST: Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia

Please initial (or mark) box if you agree:

| | |
|---|---|
| I confirm that I have read/ been read the patient information sheet (version 4.1 dated 14 August 2014) for the ARREST study and that I understand what will be required of me if I participate in the study. The study has been explained to me and I have had an opportunity to ask any questions I have about the study. | |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. | |
| I understand that sections of any of my medical notes may be looked at by responsible individuals involved in the running of the study or from the Medicines and Healthcare products Regulatory Agency where it is relevant to my taking part in research. I give permission for these individuals to have access to my records, but understand that strict confidentiality will be maintained. | |
| I understand that I will be given rifampicin or a placebo for 2 weeks while I am in the ARREST study, and then be followed by study doctors and nurses for another 10 weeks (12 weeks in total). | |
| I agree to allow the ARREST team to obtain information about my wellbeing from my electronic NHS hospital notes after these 12 weeks | |
| I agree to allow blood samples to be taken and stored for later testing. I understand that I will not be given the results of tests performed on stored samples. | |
| I agree that my GP can be told that I am taking part in this study and can be contacted about my wellbeing. | |
| I agree to take part in the ARREST study. | |

The following parts of the ARREST study are optional: please tick yes or no to indicate whether you agree

| | |
|---|---|
| **OPTIONAL**: I agree that my stored blood samples can be used for human genetic testing relating to *S. aureus* infection. I understand that I will not be given the results of tests performed on stored samples. | ☐ Yes<br>☐ No |

**<centres where PK/PD study is not recruiting to delete the rows below>**

| | |
|---|---|
| **OPTIONAL**: I confirm that I have read/ been read the patient information sheet (version 4.1 dated 14 August 2014) for the substudy on drug concentrations and bacterial killling in blood and that I understand what will be required of me if I participate in the study. The study has been explained to me and my questions have been answered. | ☐ Yes<br>☐ No |
| **OPTIONAL**: I agree to take part in the sub-study on drug concentrations and bacterial killing in blood. | ☐ Yes<br>☐ No |

| Participant’s signature | Print name | Date (day/month/year) |
|---|---|---|
| | | |

| Signature of person delegated to take consent | Print name | Date (day/month/year) |
|---|---|---|

| | | |
|---|---|---|
| | | |

**IMPORTANT: one signed original to be kept in ARREST trial file by the researcher**
**one signed copy to be given to the patient**
**one signed copy to be kept in the clinic file**

## - Legal Representative -

(To be presented on local-headed paper: same version as for trial participant except "my friend/relative/patient" rather than "me")
Version 4.1 Date 14 August 2014

# ARREST: Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia

Please initial (or mark) box if you agree:

| | |
|---|---|
| I confirm that I have read/ been read the patient information sheet (version 4.1 dated 14 August 2014) for the ARREST study and that I understand what will be required of my friend/relative/patient if they participate in the study. The study has been explained to me and I have had an opportunity to ask any questions I have about the study. | |
| I understand that my friend/relative/patient's participation is voluntary and that I am free to withdraw them at any time, without giving any reason, without their medical care or legal rights being affected. | |
| I understand that sections of any of my friend/relative/patient's medical notes may be looked at by responsible individuals involved in the running of the study or from the Medicines and Healthcare products Regulatory Agency where it is relevant to their taking part in research. I give permission for these individuals to have access to my friend/relative/patient's records, but understand that strict confidentiality will be maintained. | |
| I understand that my friend/relative/patient will be given rifampicin or a placebo for 2 weeks while they are in the ARREST study, and then be followed by study doctors and nurses for another 10 weeks (12 weeks in total). | |
| I agree to allow the ARREST team to obtain information about my friend/relative/patient's wellbeing from their electronic NHS hospital notes after these 12 weeks | |
| I agree to allow blood samples to be taken from my friend/relative/patient and stored for later testing. I understand that I and my friend/relative/patient will not be given the results of tests performed on stored samples. | |
| I agree that my friend/relative's GP can be told that my friend/relative/patient is taking part in this study and can be contacted about their wellbeing. | |
| I agree that my friend/relative/patient can take part in the ARREST study. | |

The following parts of the ARREST study are optional: please tick yes or no to indicate whether you agree

| | |
|---|---|
| **OPTIONAL**: I agree that my friend/relative/patient's stored blood samples can be used for human genetic testing relating to *S. aureus* infection. I understand that I and my friend/relative/patient will not be given the results of tests performed on stored samples. | ☐ Yes<br>☐ No |

**<centres where PK/PD study is not recruiting to delete the rows below>**

| | |
|---|---|
| **OPTIONAL**: I confirm that I have read/ been read the patient information sheet (version 4.1 dated 14 August 2014) for the substudy on drug concentrations and bacterial killling in blood and that I understand what will be required of my friend/relative/patient if they participate in the study. The study has been explained to me and my questions have been answered. | ☐ Yes<br>☐ No |
| **OPTIONAL**:I agree that my friend/relative/patient can take part in the sub-study on drug concentrations and bacterial killing in blood. | ☐ Yes<br>☐ No |

| Legal representative's signature | Print name | Date (day/month/year) |
|---|---|---|
| | | |

| Signature of person delegated to take consent | Print name | Date (day/month/year) |
|---|---|---|

| | | |
|---|---|---|

| | |
|---|---|
| Participant's Name | |

**IMPORTANT: one signed original to be kept in ARREST trial file by the researcher**
**one signed copy to be given to the patient's legal representative**
**one signed copy to be kept in the clinic file**

# APPENDIX IV - GP LETTER

Version 3.0, dated 14 August 2014

(To be presented on local-headed paper)

<date>

Dear Dr X,

Re: ARREST: Adjunctive Rifampicin to Reduce Early mortality from STaphylococcus aureus bacteraemia (ISRCTN37666216; MREC: 12/LO/0637)

Patient Name
Date of Birth xx xxxx 19xx
NHS Number xxx xxx xxxx
Hospital Number xxx xxxx

Your patient (or their legal representative where appropriate) has consented to join the above trial and has given permission to notify you of their participation in the trial.

This is a randomised, blinded, placebo-controlled clinical trial of 14 days of adjunctive rifampicin for the treatment of *S. aureus* bacteraemia, in addition to standard antibiotic therapy. This trial aims to determine whether the addition of 14 days rifampicin to initial standard antibiotic therapy reduces (i) all-cause mortality through 14 days and (ii) bacteriological failure/death through 12 weeks from randomisation in patients with *S. aureus* bacteraemia. All patients will be followed for 12 weeks.

Please find enclosed a copy of the patient information sheet for this trial. If you have any concerns or questions regarding this study please contact the responsible doctor:

Dr _____ at _____(Hospital)

Tel: _____

Yours sincerely,

Name
Position

# APPENDIX V - EQ-5D QUESTIONNAIRE

## Describing your own health today

**By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.**

**Mobility**

- I have no problems in walking about ❑
- I have some problems in walking about ❑
- I am confined to bed ❑

**Self-Care**

- I have no problems with self-care ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

**Usual Activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ❑
- I have some problems with performing my usual activities ❑
- I am unable to perform my usual activities ❑

**Pain/Discomfort**

- I have no pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have extreme pain or discomfort ❑

**Anxiety/Depression**

- I am not anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am extremely anxious or depressed ❑

# APPENDIX VI - TOXICITY GRADINGS AND MANAGEMENT

Common Toxicity Criteria for Adverse Events
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
ULN = Upper Limit of Normal ; LLN = Lower Limit of Normal

**General Instructions:**
If the need arises to grade a clinical adverse event (AE) that is not identified in the table, use the category "Estimating Severity Grade" located at the top of the table.

If the severity of an AE could fall under either one of two grades (e.g. the severity of an AE could be either Grade 2 or Grade 3) select the higher of the two grades for the AE.

**Definitions:**

| | |
|---|---|
| Basic Self-care Functions | Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. |
| Usual Social & Functional Activities | Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby etc. |

# APPENDIX VII - QUESTIONNAIRE FOR NON-CONSENTING PATIENTS AND LEGAL REPRESENTATIVES WHO ARE NOT HEALTHCARE PROFESSIONALS

We understand that you have decided not to join the ARREST study. This will make no difference to the care you receive.

We fully appreciate that you did not wish to participate in the study. However we would very much like to try and understand a bit more about why some people did not want to or felt unable to take part in the this study. It would be helpful if you could take a few minutes to tell us the reasons why. Please ignore any questions you do not want to answer.

This questionnaire is completely anonymous; no one in the hospital will ever see it. Please send the questionnaire directly to the Trials Unit running the study using the stamped addressed envelope provided. You can return the questionnaire at any time now or in the future. We will take the return of this questionnaire as consent to participate in this questionnaire study.

Your honest views and opinions are important to us: please feel free to tell us anything about your experience. Any information you give us will be used to improve how we approach people for ARREST and other trials in the future.

Question 1: were any of the following important in making your decision **not** to join ARREST? (tick one box per line: please ignore any questions you do not wish to answer)

| | not important at all | a bit important | very important | not applicable to me |
|---|---|---|---|---|
| Just don't want to take part in any research study | ☐ | ☐ | ☐ | ☐ |
| Everything else going on was too much | ☐ | ☐ | ☐ | ☐ |
| Did not feel I could make a decision either way | ☐ | ☐ | ☐ | ☐ |
| Did not feel I should make a decision for my relative/friend | ☐ | ☐ | ☐ | ☐ |
| Did not like the idea of being a human guinea pig | ☐ | ☐ | ☐ | ☐ |
| Did not think the nurse/doctor explained well enough | ☐ | ☐ | ☐ | ☐ |
| Felt too ill/tired | ☐ | ☐ | ☐ | ☐ |
| Felt too worried | ☐ | ☐ | ☐ | ☐ |
| Did not understand what would really be involved | ☐ | ☐ | ☐ | ☐ |
| Did not have enough time to decide | ☐ | ☐ | ☐ | ☐ |
| Had questions that I didn't feel I could ask | ☐ | ☐ | ☐ | ☐ |

| | | | | |
|---|---|---|---|---|
| or was embarrassed to ask | | | | |
| Worried that if I/my relative/friend joined I could not change my mind later (feeling trapped) | □ | □ | □ | □ |
| Worried that I/my relative/friend might **not get** rifampicin (the study drug) | □ | □ | □ | □ |
| Worried that I/my relative/friend might **get** rifampicin (the study drug) | □ | □ | □ | □ |
| Too much responsibility | □ | □ | □ | □ |
| Safer to just say no | □ | □ | □ | □ |
| The information sheet was unclear | □ | □ | □ | □ |
| The consent form was unclear | □ | □ | □ | □ |

Any other reasons: _____

_____

_____

_____

Question 2: would any of the following have helped you feel happier about joining ARREST? (tick one box per line: please ignore any questions you do not wish to answer)

| | not important at all | a bit important | very important | not applicable to me |
|---|---|---|---|---|
| More time to decide | □ | □ | □ | □ |
| Shorter information sheet | □ | □ | □ | □ |
| More opportunity to ask questions | □ | □ | □ | □ |
| Clearer answers | □ | □ | □ | □ |
| Clearer consent form | □ | □ | □ | □ |

Any other important things that would have helped: _____

_____

_____

_____

Question 3: Please select one of the following statements
□ I had an infection and was asked about joining ARREST myself
□ I was asked about a relative/friend joining ARREST

If you have any other thoughts or comments about the study we'd really like to hear about them here.

_____

_____

_____

_____

_____

_____

_____

_____

_____

We are very grateful for you taking the time to complete this questionnaire.

**In Guy's & St Thomas's NHS Trust only**

If you would be interested in talking further about your experiences, our patient and public advisor in ARREST would be happy to talk to you some more about what you've said above. This could either be in person at Guy's and St Thomas's hospital, or over the telephone at a time that suited you. The interview will only be asking about some more details similar to the questions about why you did not want to participate in the research study. It will take no longer than 30 minutes. The answers given in the interview will also be anonymised so that no one will be able to link your name to the answers apart from the interviewer.

Would you like to be interviewed? □ No □ Yes

Only if yes (so that the patient and public representative can contact you):

Name: Telephone Number:

Signature: Date:

Best time to call (eg. Wednesday mornings) to arrange to meet at Guy's and St Thomas's or to arrange a time to speak for up to 30 mins

## APPENDIX VIII – QUESTIONNAIRE FOR NON-CONSENTING HEALTHCARE PROFESSIONALS

The ARREST study team very much appreciates your time and effort for this study. As part of our learning we would like to try and find out if there are any barriers to recruiting and consenting patients. To do this we would be very grateful if you will spare a few minutes to answer these questions. Any that you do not want to answer please leave blank and any additional comments you have about the recruiting/consenting process please add in the box at the end.

This questionnaire is completely anonymous; no one in the hospital will ever see it. Please send the questionnaire directly to the Trials Unit running the trial using the stamped addressed envelope provided. You can return the questionnaire at any time now or in the future. We will take the return of this questionnaire as consent to participate in this questionnaire study

Question 1: were any of the following important in making your decision as a Professional Legal Representative, that a patient with Staphylococcus aureus should **not** join ARREST?
(tick one box per line: please ignore any questions you do not wish to answer)

| | not important at all | a bit important | Very important | not applicable to me |
|---|---|---|---|---|
| Thought that this patient should definitely receive rifampicin | ☐ | ☐ | ☐ | ☐ |
| Thought that this patient should definitely **not** receive rifampicin | ☐ | ☐ | ☐ | ☐ |
| Did not think this trial was right for the patient for reasons other than the intervention (rifampicin) | ☐ | ☐ | ☐ | ☐ |
| Do not believe in research in general | ☐ | ☐ | ☐ | ☐ |
| Felt I should not be asked to do this | ☐ | ☐ | ☐ | ☐ |
| Just too busy | ☐ | ☐ | ☐ | ☐ |
| Don't fully understand the study | ☐ | ☐ | ☐ | ☐ |
| Uncomfortable about asking questions of the study team | ☐ | ☐ | ☐ | ☐ |
| Unsure about the role of legal representatives | ☐ | ☐ | ☐ | ☐ |
| Did not agree with the study design, aims, methodology | ☐ | ☐ | ☐ | ☐ |

Any other reasons, and any comments on how they might be addressed: Please use this section to enter new suggestions or elaborate on those above _____

_____

_____

_____

_____

_____

Question 2: would any of the following have helped you feel happier about recruiting patients and/or giving legal representative consent for specific patients to join ARREST? (tick one box per line: please ignore any questions you do not wish to answer)

| | not important at all | a bit important | very important | not applicable to me |
|---|---|---|---|---|
| More time to decide | □ | □ | □ | □ |
| Shorter information sheet | □ | □ | □ | □ |
| More opportunity to ask questions | □ | □ | □ | □ |
| Clearer answers | □ | □ | □ | □ |
| Clearer consent form | □ | □ | □ | □ |

Any other important things that would help to improve the recruitment process: Please use this section to enter new suggestions or elaborate on those above. _____

_____

_____

_____

Please use the space to let us know anything else about your experience of being asked to be a Professional legal representative for the ARREST trial.

_____

_____

_____

_____

_____

_____

_____

_____

_____

We are very grateful for you taking the time to complete this questionnaire.

## APPENDIX IX – INFORMATION SHEETFOR CONSENTING PATIENTS OR LEGAL REPRESENTATIVES

Thank you for joining and continuing in the ARREST study.

We appreciate that we asked you about the study at a time when there was a lot going on. We would like to ask you some more about your experience of this process – and find out a bit more about why you decided to join the trial and the pros and cons of being involved.

We would particularly like to understand more about your feelings about staying in the study, so that we can improve how we do studies like ARREST in the future, and also how we do ARREST for future patients.

If you would be interested, our patient and public advisor in ARREST would like to offer you the opportunity to talk to her about your experiences in ARREST. This could either be in person at Guy's and St Thomas's hospital, or over the telephone at a time that suited you. The interview will just be asking about some questions about how you were asked about joining ARREST, why you decided to join the research study, and your experiences of being in the study. It will take no longer than 30 minutes. The answers given in the interview will also be anonymised so that no one will be able to link your name to the answers apart from the interviewer.

Your views are important to us: any information you give us will be used to improve how we approach people for ARREST and other trials in the future, and how we run the studies.

Would you like to be interviewed? □ No □ Yes

Only if yes (so that the patient and public representative can contact you):

Name: Telephone Number:

Signature: Date:

Best time to call (eg. Wednesday mornings) to arrange to meet at Guy's and St Thomas's or to arrange a time to speak for up to 30 mins