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Title page

ARREST

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

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Abstract

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Background: *Staphylococcus aureus* bacteraemia is a common, frequently fatal infection. Adjunctive rifampicin may enhance early *S. aureus* killing, sterilise infected foci and blood faster, and thereby reduce the risk of dissemination, metastatic infection and death.

Objectives: To determine whether adjunctive rifampicin reduces bacteriological (microbiologically-confirmed) failure/recurrence or death through 12 weeks from randomisation. Secondary objectives included evaluating the impact of rifampicin on all-cause mortality, clinically defined failure/reccurrence or death, toxicity, resistance emergence, and duration of bacteraemia; and assessing rifampicin's cost-effectiveness.

Design: Parallel group, randomised (1:1), blinded, placebo-controlled multi-centre trial.

Setting: UK NHS Trust Hospitals.

Participants: Adult inpatients ($\geq$18 years) with methicillin resistant or susceptible *S. aureus* grown from $\geq$1 blood culture, who had received $\leq$96 hours of antibiotic therapy for the current infection, and without contraindications to rifampicin.

Interventions: Adjunctive rifampicin (600-900mg/day; oral or intravenous) or placebo for 14 days in addition to standard antibiotic therapy. Investigators and patients were blinded to trial treatment. Follow up was for 12 weeks (assessments at 3, 7, 10, and 14 days, weekly until discharge, final assessment 12 weeks post-randomisation).

Main outcome measures: The primary outcome was all-cause bacteriological (microbiologically-confirmed) failure/recurrence or death through 12 weeks from randomisation.

Results: Between December 2012 and October 2016, 758 eligible participants from 29 United Kingdom hospitals were randomised: 370 to rifampicin and 388 to placebo. The median (interquartile range) age was 65(50-76) years. 485(64.0%) infections were community-acquired and 132(17.4%) nosocomial; 47(6.2%) were caused by methicillin-resistant *S. aureus*. 301(39.7%) had an initial deep infection focus. Standard antibiotics were given for median(IQR) 29(18-45) days; 619(81.7%) received flucloxacillin. By 12-weeks, 62/370 (16.8%) rifampicin versus 71/388 (18.3%) placebo participants experienced bacteriological (microbiologically-confirmed) failure/recurrence or died (absolute risk difference=-1.4% (95% confidence interval -7.0%-4.3%); hazard-ratio=0.96 (0.68-1.35) p=0.81). Comparing rifampicin with placebo there were 4(1.1%) versus 5(1.3%)

bacteriological failures (p=0.82), 3(0.8%) versus 16(4.1%) bacteriological recurrences (p=0.01), and 55(14.9%) versus 50(12.9%) deaths without bacteriological failure/recurrence respectively (p=0.30). Over 12-weeks, there was no evidence of differences in clinically-defined failure/recurrence/death (p=0.84), all-cause mortality (p=0.60), serious (p=0.17) or grade-3/4 (p=0.36) adverse events. However, 63(17.0%) rifampicin versus 39(10.1%) placebo experienced antibiotic or trial-drug-modifying adverse events (p=0.004) and 24(6.5%) versus 6(1.5%) respectively experienced drug-interactions (p=0.0005). Evaluation of the costs and Health Related Quality of Life impacts revealed that an episode of *S. aureus* bacteraemia costs £12 197 on average over 12 weeks. Rifampicin was estimated to save 10% of episode costs (P=0.14). After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (SE=0.004 QALY).

Limitations: Reflecting clinical practice, participants were heterogeneous in disease severity, limiting ability to investigate some clinically relevant subgroups. A minority initiated open-label rifampicin or stopped blinded trial drug early, predominantly for drug-drug interactions or adverse events.

Conclusions: Adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

Future work: Given the substantial mortality, other antibiotic combinations or improved source management should be investigated.

Study registrations: Current Controlled Trials ISRCTN37666216; EUDRACT 2012-000344-10; and CTA: 00316/0243/001

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List of abbreviations

AE	**Adverse event**
AIC	**Akaike Information Criteria**
ALT	**Alanine transaminase**
ALP	**Alkaline phosphatase**
AST	**Aspartate aminotransferase**
BD	**Twice daily**
BNF	**British National Formulary**
CI	**Confidence interval**
CRF	**Case Report Form**
CRP	**C-reactive protein**
CT	**Computed tomography**
CTA	**Clinical Trials Authorisation**
CTC	**Common Toxicity Criteria**
CTU	**Clinical Trials Unit**
DMC	**Data Monitoring Committee**
DNA	**Deoxyribonucleic acid**
eCRF	**Electronic Case Report Form**
EDTA	**Ethylenediaminetetraacetic acid**
EQ-5D	**European Quality of Life 5 Dimensions (questionnaire)**
ERC	**Endpoint Review Committee**
EudraCT	**European Union Drug Regulatory Agency Clinical Trial**
EVPI	**Expected value of perfect information**
GCP	**Good Clinical Practice**
GLM	**Generalised Linear Model**
HDU	**High dependency unit**
HIV	**Human Immunodeficiency Virus**
HR	**Hazard ratio**
HRQoL	**Health Related Quality of Life**
ICH	**International Conference on Harmonisation of Technical Requirements for**

	Registration of Pharmaceuticals for Human Use
IMP	**Investigational medicinal product**
INB	**Incremental net benefit**
INHB	**Incremental net health benefit**
IQR	**Interquartile range**
ISRCTN	**International Standard Randomised Controlled Trial Number**
ITU	**Intensive care unit**
IV	**Intravenous**
LR	**Legal representative**
MedDRA	**Medical Dictionary for Regulatory Activities**
MRC CTU at UCL	**Medical Research Council Clinical Trials Unit at University College London**
MRI	**Magnetic resonance imaging**
MRSA	**Methicillin-resistant *Staphylococcus aureus***
MSSA	**Methicillin-sensitive *Staphylococcus aureus***
NHB	**Net health benefit**
NHS	**National Health Service**
NICE	**National Institute for Health and Care Excellence**
NNT	**Number needed to treat**
OD	**Once daily**
PD	**Pharmacodynamic**
PET	**Positron emission tomography [scan]**
PI	**Principal Investigator**
PK	**Pharmacokinetics**
PPI	**Patient and public involvement**
QALY	**Quality adjusted life year**
RD	**(Absolute) risk difference**
RNA	**Ribonucleic acid**
SAE	**Serious adverse event**
SAB	***Staphyloccocus aureus* bacteraemia**

SE	**Standard Error**
SPC	**Summary of Product Characteristics**
SUSAR	**Suspected unexpected serious adverse reaction**
TOE	**Transoesophageal echocardiography**
UCL	**University College London**
ULN	**Upper limit of normal**
UKCIRG	**United Kingdom Clinical Infection Research Group**

Plain English Summary

Staphylococcus aureus (or *S. aureus*) is a germ which can cause serious infections, particularly when it gets into the bloodstream. Doctors use an antibiotic to cure *S. aureus* but sometimes the antibiotic does not succeed in curing the infection and sometimes the infection comes back.

The ARREST trial tested whether or not giving two weeks of an extra antibiotic, called rifampicin, in addition to the standard antibiotic, would help sick people with *S. aureus* blood infections. The aim was to find out if rifampicin could cure more people, possibly faster, to see whether it caused more or less side-effects and to see if the germ that causes the infection became resistant to rifampicin.

In total, 770 patients from the United Kingdom (UK) aged 18 to 100 years participated. The participants all received the same standard antibiotic that they would have received if they had not joined the study. In addition 370 patients received two weeks of rifampicin and 388 patients received two weeks of placebo (dummy).

The ARREST study found that people who had rifampicin in addition to standard antibiotic treatment did no better overall than people who had just standard antibiotic treatment, in terms of how successful their treatment was. People in the group who had rifampicin were no more likely to have serious or severe side-effects than those in the group who had placebo. There was some evidence that rifampicin reduced the risk of the infection coming back again. But this did not reduce the overall deaths. *S. aureus* from only two people's blood developed resistance to rifampicin.

The results suggest that people with *S. aureus* blood infections are unlikely to benefit from adding rifampicin to standard antibiotic treatment. The study included a wide range of patients with *S. aureus* blood infections, so the results apply widely.

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Scientific Summary

Background

Staphylococcus aureus bacteraemia is a common and serious infection, with an associated mortality of approximately 25%. Once *S. aureus* enters the blood stream it can disseminate to infect almost any organ of the body, but most commonly affects the bones, joints and heart valves. Despite the infection's severity, the evidence guiding optimal antibiotic therapy is weak as fewer than 1500 patients have been included in 16 randomised controlled trials investigating *S. aureus* bacteraemia treatment. Therefore which antibiotics are most effective, their route of administration and duration, and whether antibiotic combinations are better than single agents is unknown. We hypothesised that adjunctive rifampicin would reduce bacteriologically-confirmed failure/recurrence or death, by enhancing early *S. aureus* killing, sterilising infected foci/blood faster, and reducing risks of dissemination and metastatic infection.

Objectives

The primary objective of the trial was to investigate the impact of adjunctive rifampicin on bacteriologically confirmed failure/recurrence or death through 12 weeks from randomisation. Secondary objectives included evaluating the impact of rifampicin on all cause mortality up to 14 days from randomisation, on clinically-defined failure/recurrence or death, toxicity (serious or grade 3 or 4 adverse events (AEs) or modification of any treatment due to drug interactions), emergence of resistance, and duration of bacteraemia; and assessing the cost-effectiveness of adjunctive rifampicin for *S. aureus* bacteraemia in the NHS.

Methods

Design:

Parallel group, randomised (1:1), blinded, placebo controlled multi-centre trial.

Setting:

29 large acute NHS Trusts. Patients were identified through the clinical microbiology laboratory and the infectious diseases/microbiology consult service at each centre.

Participants:

Inclusion Criteria:

- Adult inpatients (18 years or older)
- *Staphylococcus aureus* (methicillin-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) provided written informed consent

Exclusion criteria:

- Infection not caused by *S. aureus* alone in the opinion of the infection specialist (e.g. *S. aureus* 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*
- 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

Incapacitated adults were eligible provided they had an appropriate legal representative to provide consent.

Interventions:

Eligible patients were randomised to standard intravenous antibiotic therapy of the attending physician's choice plus either 14 days of placebo or rifampicin (900mg/24 hours if ≥60kg; 600mg/24 hours if<60kg). Rifampicin could be administered via intravenous (IV) or oral route according to patient status and either once daily (OD) or twice daily (BD).

Follow up:

All participants were followed up on days 3, 7, 10, 14, weekly until discharge, and the final assessment took place at 12 weeks post randomisation.

Sample size:

770 patients were recruited, providing 80% power 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, assuming 10% loss to follow-up by 12 weeks (two-sided alpha=0.05).

Health economics:

Cost and health outcomes for patients with *S. aureus* bacteraemia were evaluated using data from the ARREST trial. Costs considered were those incurred by the NHS and encompassed

antibiotic therapy, admissions to secondary care (including investigations and procedures undertaken while hospitalised) and consultations with healthcare providers after hospital discharge from first admission. Health outcomes were measured as quality-adjusted life years (QALYs), calculated from EQ-5D-3L responses collected in the trial and imputed to account for missingness. Costs and QALYs were measured only for 84 days (i.e. 12 weeks), the maximum duration of active follow-up. The analyses used a regression approach to explore determinants of costs and QALYs on baseline covariates, including treatment group, which allowed for a cost-effectiveness analysis to be conducted. Decision uncertainty was accounted for through probabilistic modelling.

Results

Baseline characteristics:

Between December 2012 and October 2016, 758 eligible participants from 29 United Kingdom hospitals were randomised: 370 to rifampicin and 388 to placebo. 495 (65.3%) were men. The median (interquartile range (IQR)) age was 65 (50-76) years, and Charlson co-morbidity score was 2 (0-3). 70 (9.2%) participants were in an intensive care unit. Mean (Standard Error) CRP was 164 (3.7) mg/L. 127 (16.8%) had consent provided by a legal representative due to incapacity. 485 (64.0%) infections were community-acquired, with only 132 (17.4%) nosocomial. 47 (6.2%) infections were caused by methicillin-resistant *S. aureus* (MRSA). No patients were known to have rifampicin-resistant *S. aureus* bacteraemia at randomisation. The initial focus was deep in 301 (39.7%) (including 33 (4.4%) with endocarditis and 14 (1.8%) with infected prostheses); 130 (17.2%) were due to infected central/peripheral lines; 138 (18.2%) associated with skin/soft tissue infections; another type of focus was identified in 49 (6.5%) and not established in 139 (18.3%). At randomisation, participants had received median (IQR) 62 (42-75) hours of active antibiotics.

Follow up:

22 (2.9%) participants withdrew consent. At the 12-week visit only 39 (5.1%) had unknown vital status and 65 (8.6%) were not assessed for signs/symptoms of *S. aureus* infection (including consent withdrawals).

744 (98.2%) participants initiated blinded trial drug (96 (12.7%) intravenously, 595 (78.5%) 900mg daily), a median (IQR) 68 (48-85) hours after starting active antibiotics for the current infection. Trial drug was continued for median (IQR) 12.6 (6.0-13.2) days in rifampicin participants versus 13.0 (11.3-13.5) days in placebo participants ($p<0.0001$; primarily due to antibiotic-modifying AEs and drug-drug interactions, see below). Percentages reporting

missing any doses ranged from 9.5%-16.2% but did not differ between randomised groups (global p=0.72).

A substantial variety of 'backbone' active antibiotics were used, although flucloxacillin was given in 619 (81.7%), and vancomycin or teicoplanin in 380 (50.1%) at some point in the primary treatment course. The numbers of antibiotics used (median (IQR) 3 (2-4)) and the duration of anti-staphylococcal treatment (median (IQR) 29 (18-45) days) was similar between groups. 32 (8.6%) rifampicin participants versus 52 (13.4%) placebo participants used open-label rifampicin (p=0.04), initiated median (IQR) 14 (7-18) days after randomisation. 159 placebo versus 142 rifampicin participants had a deep focus which was drained/removed in 35 (22.0%) versus 29 (20.4%), a median (IQR) 5 (2-12) and 3 (1-6) days from randomisation respectively.

Primary endpoint:

By 12-weeks, 62/370 (16.8%) rifampicin versus 71/388 (18.3%) placebo participants experienced bacteriological failure/recurrence or died (absolute risk difference (RD)=-1.4% (95% confidence interval -7.0%,+4.3%); hazard-ratio(HR)=0.96 (0.68-1.35) p=0.81). Comparing rifampicin with placebo there were 4(1.1%) versus 5(1.3%) bacteriological failures (p=0.82), 3(0.8%) versus 16(4.1%) bacteriological recurrences (p=0.01), and 55(14.9%) versus 50(12.9%) deaths without bacteriological failure/recurrence respectively (p=0.30).

Secondary endpoints:

Clinically-defined failure/recurrence or death occurred in 76 (20.5%) rifampicin versus 86 (22.2%) placebo participants (RD=-1.4% (95% CI -7.4%,+4.7%); HR=0.97 (0.71-1.32) p=0.84). Comparing rifampicin and placebo there were 23 (6.2%) versus 25 (6.4%) failures (p=0.97), 8 (2.2%) versus 23 (5.9%) recurrences (p=0.01), and 45 (12.2%) versus 38 (9.8%) deaths without clinically-defined failure/recurrence respectively (competing-risks p=0.22). By 12-weeks, 56 (15.1%) rifampicin versus 56 (14.4%) placebo participants died (RD=+1.0% (95% CI -4.3%,+6.2%); HR=1.10 (0.76-1.60) p=0.60). 25 (6.8%) rifampicin versus 17 (4.4%) placebo participants died before 2 weeks (HR=1.60 (0.86-2.95) p=0.13). 14 rifampicin versus 16 placebo deaths were adjudicated definitely *S. aureus*-related, 14 versus 12 probably *S. aureus*-related, and 8 versus 4 possibly *S. aureus*-related, respectively. 18 versus 23 were not attributed to *S. aureus* (remainder unattributable) (overall p=0.64). There was no difference in longer-term (post-week 12) survival between the groups (p=0.69). There was no evidence that duration of bacteraemia was significantly shorter in those randomised to rifampicin (global p=0.66). Two (0.5%) rifampicin participants developed new rifampicin-resistant *S. aureus*

bacteraemia 7 and 42 days after randomisation (p=0.24). One occurred on day 7 (followed by rifampicin discontinuation on day 11 and bacteriological failure on day 14); the other on day 42 (prescribed 14 days rifampicin; bacteriological recurrence on day 42).

Safety:

By 12-weeks, 101 (27.3%) rifampicin versus 94 (24.2%) placebo participants experienced 112 versus 116 serious adverse events (HR=1.21 (95% CI 0.92-1.61) p=0.17). Two rifampicin participants with pre-existing liver disease experienced non-fatal hepatic failure. 129 (34.9%) rifampicin versus 131 (33.8%) placebo participants experienced 209 versus 193 grade 3/4 AEs (HR=1.12 (95% CI 0.88-1.43) p=0.36). Most notable was a trend towards more renal grade 3/4 AEs with rifampicin which occurred in 19 (5.1%) versus 9 (2.3%) placebo participants (p=0.053); 17 versus 6 respectively being acute kidney injury. 63 (17.0%) rifampicin versus 39 (10.1%) placebo experienced 89 versus 52 antibiotic-modifying AEs (sub-distribution HR=1.78 (1.20-2.65) p=0.004). Gastrointestinal disorders (24 versus 8 participants, respectively, p=0.003) and renal/urinary disorders (8 versus 1 participants, respectively, p=0.02) were more common with rifampicin. 24 (6.5%) rifampicin versus 6 (1.5%) placebo experienced drug-interactions (p=0.0005); 13 versus 4 led to discontinuation of trial drug (p=0.03), 14 versus 3 respectively led to grade 1/2 AEs (p=0.006), and 5 versus 2 respectively to grade 3/4 AEs (p=0.27).

Health economics:

We found that an episode of *S. aureus* bacteraemia costs, on average, £12 197 over 12 weeks. The cost categories that contributed the most to costs were length of stay (primary hospital admission and readmissions) and procedures undertaken in hospital. Baseline determinants of higher episode costs were nosocomial *S. aureus* bacteraemia (costs 41% higher); a deep primary focus of infection (costs 43% higher); endocarditis (costs 65% higher), high neutrophil count (>9x10^9/L, costs 33% higher), and if the patient was comatose (costs 32% higher). Age, gender, BMI, Charlson index and methicillin resistance did not affect costs.

Analysis indicates that adjunctive rifampicin may save 10% of episode costs, with larger savings happening after 14 days. Despite not being statistically significant, this result is consistent with the small reduction in recurrences that probably drives shorter hospital stays. It is however, important to note that the costs of rifampicin toxicity and drug-drug interactions were not included in this analysis.

As expected in this population of acutely ill patients, very low values of the EQ5D score were observed at baseline (mean EQ-5D score of 0.10). Determinants of QALYs in the sample were baseline EQ5D score (0.0064 QALYs lost for every 0.1 decrease in baseline EQ-5D);

higher age (up to 0.044 QALY loss); Charlson index (up to 0.024 QALY loss) and coma (mean QALY loss of 0.020). After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (SE=0.004 QALY).

Conclusions

Adjunctive rifampicin does not reduce mortality from *S. aureus* bacteraemia. It may reduce the risk of disease recurrence. Our trial suggests this effect had no impact on short-term or longer-term mortality, but it may reduce costs. However, rifampicin significantly complicates other drug treatment. We therefore consider that adjunctive rifampicin provides no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

Trial registrations

Current Controlled Trials ISRCTN37666216; EUDRACT 2012-000344-10; and CTA: 00316/0243/001

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Chapter 1 Introduction

(Note: this chapter includes material that has been adapted from the trial protocol which has been published in Trials 2012 13:241)

Background

Staphylococcus aureus bacteraemia is one of the most common and serious bacterial infections worldwide. There were over 12,000 cases of *S. aureus* bacteraemia in the UK in 2016/2017, and around 25% of these patients die.[1,2] 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 methicillin-resistant. Combination antimicrobial therapy is generally not recommended, except in severe methicillin-resistant *S. aureus* (MRSA) infections (e.g. endocarditis) or in the presence of prosthetic joint infections.[3-6] Most of the recommendations are based on uncontrolled observational studies and clinical experience, and views of how to manage *S. aureus* bacteraemia differ widely.[7,8]

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, it has been 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.

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 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 Human Immunodeficiency Virus (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.

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.[29,30] 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; subgroup 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 one 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 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] A recent observational study of 964 patients with *S. aureus* bacteraemia reported 512 (53%) of them received combination therapy and the majority (301/512, 59%) received rifampicin.[33] Combination therapy was not associated with reduced mortality in all patients, but was associated with reduced deaths and infection-related complications in those suffering from device-related infections.

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).[34] Rifampicin was used to treat 21% of MRSA bacteraemia and 15% of methicillin-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).

Rationale

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 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).[4,6] But with weak support for these recommendations it is unsurprising few physicians follow them in practice. The ARREST trial was designed to provide a definitive answer to the role of adjuvant rifampicin therapy in the treatment of *S. aureus.*

Objectives

The hypothesis addressed by the ARREST trial 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 was to investigate the impact of adjunctive rifampicin on bacteriologically-confirmed failure/recurrence or death through 12 weeks from randomisation. Secondary objectives included evaluating the impact of rifampicin on all cause mortality up to 14 days from randomisation, on clinically-defined failure/recurrence or death, toxicity (serious and grade 3/4 adverse events (AEs), any modification of treatment due to drug interactions), emergence of resistance and duration of bacteraemia; and assessing the cost-effectiveness of adjunctive rifampicin for *S. aureus* bacteraemia in the NHS.

Substudies

There were three ancillary studies to the main trial. First, with assistance from the trial's public and patient representative, Jennifer Bostock, we examined the process of obtaining consent to enter the trial. Patients/legal representatives who did not consent to participation in the trial were offered the opportunity to complete a questionnaire exploring reasons for this; participants/legal representatives at one trial centre who did consent were offered the opportunity to be interviewed by the ARREST patient and public representative to explore their experiences of trial participation.

Samples were collected for two further ancillary studies for which funding will be sought seperately. Participants enrolled at Guy's & St Thomas' NHS Foundation Trust, Cambridge University Hospitals NHS Trust, Oxford Univerity Hospitals NHS Trust, The Royal Liverpool and Broadgreen University Hospitals NHS Trust and Brighton and Sussex University Hospitals NHS Trust were approached for additional consent for a pharmacokinetic/pharmacodynamic (PK/PD) substudy – a population PK/PD study of rifampicin, flucloxacillin and vancomycin for the treatment of *S. aureus*. The aim of the 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.

All participants were also approached for additional consent for the host DNA/RNA substudy to investigate the influence of host and bacterial genetics on disease severity and outcome from *S. aureus*. The 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 samples for the PK/PD and DNA/RNA substudies have been archived at the King's College London Biobank until funding has been secured.

Chapter 2 Methods

(Note: this chapter includes material that has been adapted from the trial protocol which has been published in Trials 2012 13:241.)

Trial setting

Patients were recruited from 29 large UK NHS Hospital Trusts: Guy's and St Thomas' NHS Foundation Trust; Oxford University Hospitals NHS Trust; University College London Hospitals NHS Foundation Trust; Royal Free London NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Brighton and Sussex University Hospitals NHS Trust; The Royal Liverpool and Broadgreen University Hospitals NHS Trust; Sheffield Teaching Hospitals NHS Foundation Trust; Cambridge University Hospitals NHS Foundation Trust; Royal United Hospital Bath NHS Trust; Royal Devon and Exeter NHS Foundation Trust; Plymouth Hospitals NHS Trust; Hull and East Yorkshire Hospitals NHS Trust; South Tees Hospitals NHS Foundation Trust; Heart of England NHS Foundation Trust; St George's Healthcare NHS Trust; Portsmouth Hospitals NHS Trust; University Hospital Southampton NHS Foundation Trust; Blackpool Teaching Hospitals NHS Foundation Trust; The Leeds Teaching Hospital NHS Trust; Aintree University Hospital NHS Foundation Trust; Bradford Teaching Hospitals NHS Foundation Trust; County Durham and Darlington NHS Foundation Trust; Dartford & Gravesham NHS Trust; North Cumbria University Hospitals; University Hospitals of Leicester NHS Trust; Wirral University Teaching Hospital NHS Foundation Trust; The Newcastle upon Tyne Hospitals NHS Foundation Trust; and Salford Royal NHS Foundation Trust.

The main criteria for selecting participating hospitals was that they had an existing *S. aureus* bacteraemia ward consultation service, sufficient numbers of *S. aureus* bacteraemias to be able to recruit patients (potential to recruit a minimum of one patient per month), as well as the necessary research infrastructure to conduct the trial.

The overall trial design is summarised in **Figure 1**.

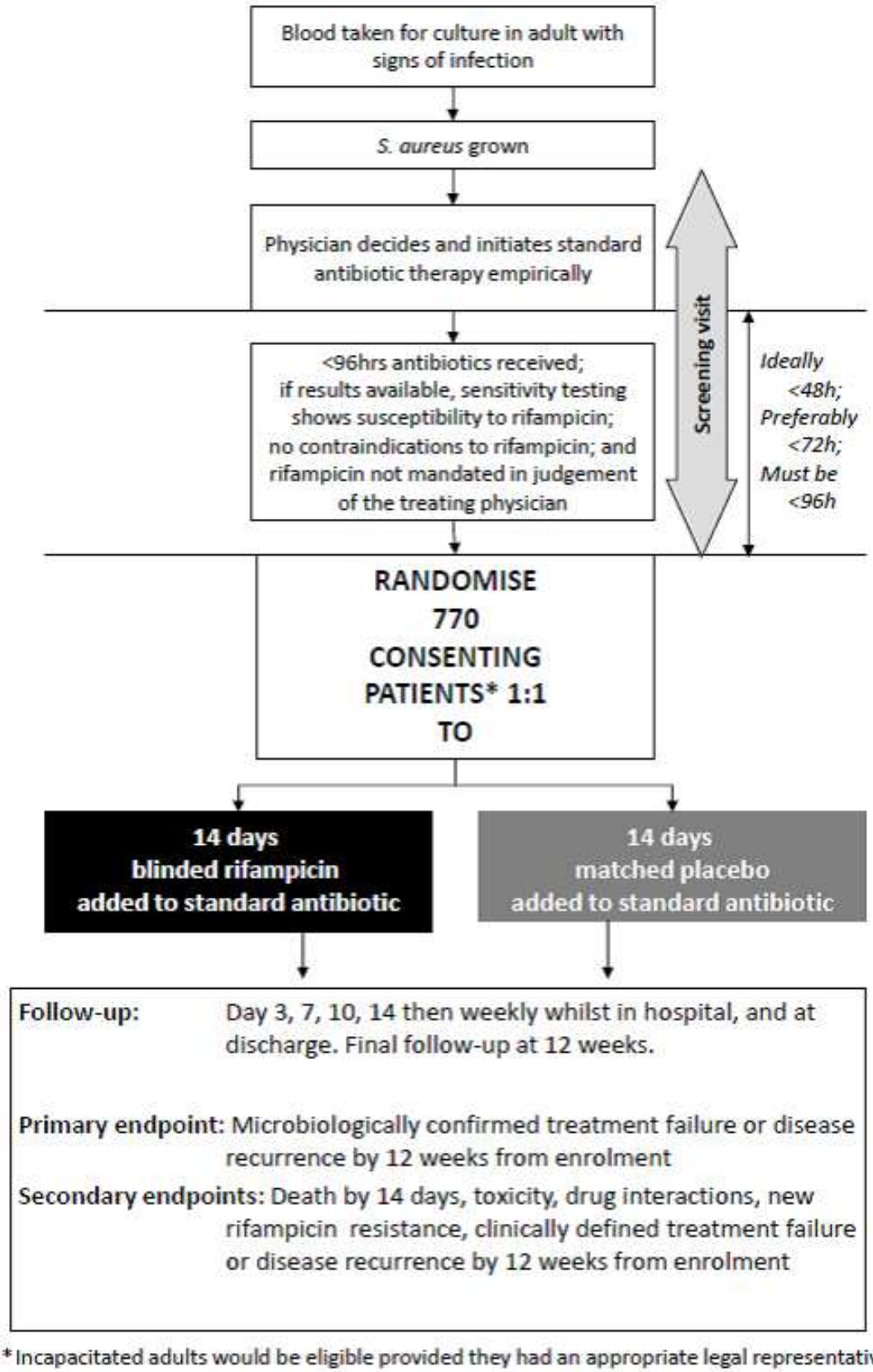


Figure 1: Trial Schema

Patient selection

As *S. aureus* bacteraemia is a serious infection whose standard treatment requires IV antibiotics, all eligible patients were hospital inpatients at the time of recruitment. Patients were identified via the clinical microbiology laboratory and the infectious diseases/microbiology consult service at each centre. When possible, patients were screened for eligibility on the day that their blood cultures flagged positive with *S. aureus*. Written informed consent was obtained from patients. Incapacitated adults were eligible provided they had an appropriate legal representative (LR) to provide consent. The Principal Investigator (PI) or another experienced independent physician was required to 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 was confirmed, then written informed consent was 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).

INCLUSION CRITERIA

The trial enrolled adults aged 18 years or older who had *S. aureus* (methicillin-susceptible or resistant) grown from at least one blood culture, had received less than 96 hours of active antibiotic therapy for the current infection (not including rifampicin, and excluding any stat doses), and the patient or LR had provided written informed consent for participation in the trial.

Although the formal inclusion criteria stated that patients must have received <96 hours of active antibiotic therapy for the current infection, 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] Therefore, patients were included in the trial as soon after initiation of active antibiotic therapy as possible, within 48 hours wherever possible and ideally within 72 hours.

EXCLUSION CRITERIA

Patients were excluded from the trial if they had infection not caused by *S. aureus* alone in the opinion of the infection specialist (e.g. *S. aureus* was considered a blood culture contaminant, or polymicrobial culture with another organism likely to be contributing clinically to the current infection); if sensitivity results were already available and demonstrated rifampicin resistant *S. aureus* (defined by British Society for Antimicrobial Chemotherapy *in vitro* disc susceptibility testing or by Vitek testing); if the infection specialist, in consultation with the treating physician, considered rifampicin to be contraindicated for any reason; if the infection specialist, in consultation with the treating physician, considered rifampicin treatment to be mandatory for any reason; if the infection specialist suspected active infection with *Mycobacterium tuberculosis;* or if the patient had been previously been randomised in ARREST for a prior episode of *S. aureus* bacteraemia.

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

Randomisation

Eligibility was confirmed by ARREST site investigators (PI, co-principal investigator, or research nurse) via the online ARREST database, and patients were randomised into two parallel groups in a 1:1 ratio, to standard intravenous antibiotic therapy plus 14 days placebo, or standard intravenous antibiotic therapy plus 14 days rifampicin. The choice and duration of the standard antibiotic therapy was left to the attending physician. Randomisation was stratified by clinical centre, as blinded drug (in fully made-up and labelled treatment packs) was pre-shipped to local pharmacies. A computer-generated sequential randomisation list using variably-sized permuted blocks was prepared by the trial statistician and incorporated securely into the online trial database. The list was concealed until allocation, after eligibility was

confirmed by researchers at the local hospitals, who then performed the randomisation. A 24 hour web-based randomisation service was provided via the online ARREST database.

Trial Intervention

Rifampicin/placebo was given by oral or intravenous route, according to the attending physician's preference and the patient's status. Provided a patient could swallow safely, the preference was to use rifampicin orally. Intravenous administration was permitted for patients that were not able to swallow or absorb tablets. Rifampicin is a well-established, widely used drug, and was not used outside its licensed indication during the course of the trial.

The oral Investigational Medicinal Product (IMP) was prepared by a Clinical Trials Supplier (Sharp Clinical Services). It was supplied as rifampicin 300 mg capsules (Sanofi-Aventis, UK) Summary of Product Characterisitics (SPC): http://www.medicines.org.uk/emc/medicine/21223/SPC/Rifadin+300mg+Capsules/, or placebo oral 300mg capsules containing cellulose. The placebo capsules were over-encapsulated so that they were identical in appearance to the rifampicin capsules. The capsules were supplied to trial centres as individual participant blinded treatment packs so they were dosed and dispensed in the same way.

The IV IMP was provided via standard hospital stock and consisted of either rifampicin for intravenous infusion (Rifampicin 600 mg for intravenous injection (Sanofi-Aventis, UK) SPC http://www.medicines.org.uk/emc/medicine/6435), or standard saline as the placebo. Participants receiving intravenous infusions in the intensive care unit could have their infusion volume altered in accordance with standard local practice and the SPC. The trial pharmacist at each hospital had access to a copy of the randomised allocations for each ARREST trial number for their centre in order to prescribe IV rifampicin if required.

DOSE

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

- those <60kg received 600mg every 24 hours
- those ≥60kg received 900mg every 24 hours

Oral doses could be given once or twice daily, according to clinician and patient preference, and subgroup analysis according to initial oral dosing frequency (elicited at randomisation) was pre-specified. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm): as rifampicin can also be taken once daily, this provided adequate exposure.

Where IV was prescribed, it was administered to the patient over 2-3 hours.

BLINDING AND MASKING

Rifampicin for intravenous infusion is supplied as a vial of red powder that requires reconstitution with 10 ml of water for infusion with saline. The resulting fluid for intravenous infusion is orange. It was impossible to safely and reliably produce a red-powder placebo which produced an identical orange infusion. Therefore, the ward nurse making up the intravenous drug for the infusion was not blind to the treatment, nor was the hospital pharmacist dispensing either rifampicin or saline for IV administration. The ward nurses were instructed not to divulge the colour of the drug to the physicians caring for the patient. In addition, the infusion was covered by an opaque bag to disguise the treatment. As far as possible the trial physicians, research nurses, and other physicians caring for the patient remained blinded, as were all trial and data management staff except for statisticians.

Rifampicin can turn urine (and tears/sweat) reddish-orange. It is impossible to safely replicate this effect with a placebo; therefore urine discolouration was a potential source of unblinding, particularly of the participant. There is, however, considerable inter- and intra-individual variability in rifampicin's effect on urine colour. In addition, the opportunity for physicians to examine the urine at the bedside only occurred in participants with urinary catheters. Catheters were not required by all participants and were removed at the earliest opportunity. We also limited the opportunity for physicians to inspect urine by ensuring the catheter bags were emptied regularly and urine was not allowed to accumulate in large volumes. The success of blinding was assessed at the final 12 week visit, when physicians and participants were asked which treatment they believed they had received.

DOSE MODIFICATIONS, INTERRUPTIONS AND DISCONTINUATIONS

Toxicity was managed in both randomised groups according to standard clinical practice. In some situations, changes in the patient's condition meant that the dose of rifampicin needed to be reduced or stopped altogether. Wherever possible, this was done without unblinding. Unblinding was only performed when knowledge of the allocated treatment had a direct bearing on clinical management. Patients were not put at any additional risk by trial randomisation, as any patient that developed a suspected adverse drug reaction to study drug was managed as if they were receiving rifampicin, and study drug was discontinued.

The most important rifampicin toxicity is liver impairment, although serious hepatic toxicity is rare (<1% of patients). The study drug (rifampicin/placebo) was withdrawn without unblinding if significant liver toxicity was observed (blood Aspartate aminotransaminase (AST)/Alanine transaminase (ALT) >5x upper limit of normal (ULN)) without other probable causes, and was withdrawn for grade 4 liver toxicity (blood AST/ALT > 10xULN) regardless of probable cause. The dose of study drug was reduced if less severe liver dysfunction occured according to the judgement of the treating physician. Other medications (including other antibiotics) were 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 was not mandated for patient management.

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).

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

- where other antibiotics being used to treat *S. aureus* bacteraemia were 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 became available after the patient had been randomised and initiated rifampicin/placebo and indicated resistance to rifampicin. This was to prevent any toxicity from an additional but ineffective drug

being used. Primary rifampicin resistance was expected in <1% enrolled patients based on observational study data.[34]

OTHER ANTIBIOTICS

Infection specialist consultation, with advice on management to non-specialists caring for the trial participants, followed normal clinical practice in all sites. Attending physicians could change 'backbone' antibiotics according to clinical need and infection specialist advice and use open-label rifampicin after 14 days; where judged clinically necessary they could stop blinded trial drug before 14 days to use open-label rifampicin, with participants continuing follow-up "off study drug, on study".

Assessments and follow-up

TRIAL ASSESSMENT SCHEDULE

All participants were followed by the centre trial teams for 12 weeks for evaluation of all-cause mortality, morbidity and toxicity. To assess the outcome measures, patients were visited on the ward by the centre PI, one of their clinical team (e.g. Specialist Registrar), or a research nurse. The schedule for timing, frequency and method of collection of all study data is summarised below. Assessments were performed as close as possible to the required time point.

SCREENING AND RANDOMISATION VISITS

Patients were identified through the clinical microbiology laboratory and the infectious diseases/microbiology consult service of each centre. All the trial centres ran a clinical consult service for all cases of *S. aureus* bacteraemia and identified such patients as soon as their blood cultures become positive. The screening visit took place as soon as possible after a potential patient had 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 was essential that patients were 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 patient consent to recruitment was requested within two hours of the screening assessment wherever possible, and ideally within four hours.

Written informed consent to enter into the trial and be randomised was obtained from patients or a person with responsibility (including legal authorities) (a legal representative, LR).

After consent was obtained from the patient or their legal representative, clinical information including medical history and examination, and weight were recorded. C-reactive protein (CRP) and liver function tests are routine investigations for patients with suspected *S. aureus* bacteraemia and were also recorded

Randomisation took place as soon as possible after eligibility was confirmed and consent was signed.

FOLLOW UP

At each main clinical assessment (days 0, 3, 7, 10, 14, weekly until discharge, week 12 final visit), the following was 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
- 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 were recorded. With the exception of events leading to modification/interruption/discontinuation of the study drug, the severity and likely relationship of these adverse events to rifampicin/placebo was documented by a physician. Any drug interactions leading to dose modification of any drug (including concomitant medications) were also be recorded.
- Assessment of adherence to rifampicin/placebo (missed pills)
- Assessment of resource utilisation (medications, procedures, laboratory tests and other relevant resource use categories)

Blood cultures were 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 could be taken at any other timepoints necessary for clinical management: but were additionally taken if potential treatment failure is suspected (e.g. in patients who still had a positive blood culture on day 7 and in whom transoesophageal echocardiography (TOE) was being considered) or where *S. aureus* bacteraemia recurrence was suspected. C-reactive protein was measured on days 0, 3, 10 and 14 to assess treatment response. ALT, bilrubin, alkaline phosphatase was assessed on days 3 and 10 to evaluate liver toxicity. Full blood count was 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) were taken from patients on day 0 stored for later DNA/RNA extraction where consent had been provided for this. If a patient had already been discharged from hospital before day 7, 10, or 14, these additional investigations requiring a blood draw (culture, CRP, ALT (Alkaline phosphatase), ALP, bilirubin, serum storage) were not required so patients were not asked to attend ARREST specific outpatient appointments on these days, but returned at 12 weeks only.

EQ-5D for quality of life assesment was administered on days 0, 7, 14 and at the final visit.

Those patients discharged before 12 weeks were managed and followed-up through each centre's infectious diseases outpatient clinic. Final follow-up at 12 weeks was either by a ward visit (if the patient was still admitted to hospital) or by a clinic visit with interview and clinical assessment. In the event that the patient was unable to attend clinic, the follow-up visit could take place over the phone. If failure or *S. aureus* bacteraemia recurrence was suspected then repeat blood cultures were performed together with a clinical assessment and EQ-5D.

The trial end was defined as the final 12 week visit of the last patient to be randomised. At the end of the trial, vital status of all participants was ascertained from electronic NHS records, and consent was sought for this.

Procedures for assessing efficacy

The trial's primary outcome was:

- Time to death or bacteriologically confirmed failure or disease recurrence up to 12 weeks from randomisation

This outcome measure was 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 or telephone call). Consent to contact the patient's GP was also obtained.

The definition of bacteriologically confirmed failure was:

(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 bacteriologically confirmed disease recurrence was :

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

As defined, failure reflected both the speed of killing of *S. aureus* and sterilisation of infected foci/blood, and both failure and recurrence reflected the risk of dissemination and metastatic infection. Outcome measures included *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 was not considered failure. Additional blood cultures were requested as soon as the PI/study physician suspected failure or recurrence. All bacterial isolates (initial and all subsequent) from patients randomised in the trial were originally intended to be genotyped by multi-locus sequence and spa-typing and tested for susceptibility to rifampicin.

A substantial proportion of bacteriological failure/recurrences did not have both baseline and failure/recurrence isolates stored (17 (61%) of 28 failures/recurrences where *S. aureus* was isolated from a sterile site). In order to avoid excluding a substantial proportion of potential primary endpoints, the statistical analysis plan specified that the primary analysis would

include all bacteriologically-confirmed failures and recurrences (i.e. without restricting to the same strain).

In the 11 pairs of baseline and failure/recurrence isolates that were stored, same strain was defined by whole-genome-sequencing using Illumina technology on the basis of 40 single nucleotide variants between baseline and failure/recurrence isolates. All failure/recurrence isolates were within 12 single nucleotide variants of the baseline isolate (median 1 (IQR 1-6) (range 0-12)).

The secondary efficacy outcome measures were:

- time to all cause mortality up to 14 days
- time to clinically defined failure or recurrence or death by 12 weeks
- duration of bacteraemia
- 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) (all AEs reported, primary comparisons based on time to first event)
- The proportion modifying any treatment (including concomitant medications) due to drug interactions
- The proportion developing rifampicin resistant *S. aureus*
- Cost-effectiveness of rifampicin

Mortality was reported on the ARREST database on a Serious Adverse Event (SAE) electronic Case Report Form (eCRF). Clinically defined failure or recurrence was assessed clinically in the same manner as bacteriologically confirmed failure or recurrence; however, microbiological confirmation was not required (for example, patients who failed clinically but where blood cultures were not taken). Clinically defined failure/recurrence was primarily 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.

PIs were required to report all potential failures/recurrences and they were adjudicated as trial endpoints by an independent endpoint committee. The blinded independent review committee consisted of two infectious disease physicians with experience in acute/general medicine (Professor Tim Peto, Oxford; Dr Graham Cooke, Imperial; see acknowledgements). Potential

failures/recurrences were also identified through questions regarding signs and symptoms of ongoing or new *S. aureus* infection on routine case record forms, and *S. auerus* isolated from any microbiological specimen. For all such potential failures/recurrences a structured clinical narrative was completed by the site physician and approved by the site PI. All reported failures, recurrences and deaths were then adjudicated using standardised proformas by the committee without knowledge of randomised allocation.

Blood cultures were taken on days 3 and 7 following randomisation to assess duration of bacteraemia. Sensitivity to rifampicin was repeated on the day 3 and 7 blood cultures, and in all subsequent *S. aureus* isolates grown at scheduled timepoints or at failure/recurrence, in order to assess the secondary endpoint, development of rifampicin resistant *S. aureus*.

CRP was measured longitudinally as a continuous measure of response to infection.

Procedures for assessing safety

Hepatitis is the most important side effect of rifampicin. Liver function tests were performed twice whilst on rifampicin/placebo (day 3 and 10) to assess laboratory safety parameters. Additional safety blood tests or investigations were performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Grade 3 and 4 and serious adverse events were elicited at the regular clinical assessments, through consultation with the patient, their medical team, or their medical records. All such adverse events were reported on eCRFs, together with adverse events of any grade leading to modification of rifampicin/placebo dose or its interruption/early discontinuation. All adverse events (clinical and laboratory) were graded using the Common Toxicity Criteria (CTC) grading scale v3.0. SAEs were defined following the International Committee for Harmonization as events which led to death, were life-threatening, caused or prolonged hospitalisation (excluding elective procedures), caused permanent disability, or were other medical conditions or with a real, not hypothetical risk of one of the previous categories. SAEs were reported to the Medical Research Council Clinical Trial Unit at University College London (MRC CTU at UCL) according to standard timelines. All SAEs were reported on study eCRFs, unless they were specifically related to the *S. aureus* bacteraemia episode for which the

patient was originally admitted (in which case they were reported as infection-related events). The protocol specifically exempted events related to *S. aureus* bacteraemia from adverse event reporting, unless the event was fatal, to avoid double counting. The severity and likely relationship of any adverse events to rifampicin/placebo were documented by a physician. All reported adverse events were coded centrally at the MRC CTU at UCL using the Medical Dictionary for Regulatory Activities (MedDRA).

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

Procedures for assessing health related costs of *S. aureus* and quality of life

Healthcare-related costs of *S. aureus* bacteraemia in the NHS and the evaluation of health-related quality of life were evaluated using the EuroQol-5D questionnaire (EQ-5D). These assessments were used further to inform the cost effectiveness of adjunctive rifampicin and relevant antibiotic regimens for *S. aureus* bacteraemia (see Chapter 5 Economic and Health-Related Quality of life consequences of *S. aureus* bacteraemia, and effect of treatment with adjunctive rifampicin). Information on healthcare-related costs of patients in the trial was collected, 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) was collected at the regular clinical assessments, and data on other healthcare resource utilisation (post-discharge outpatient visits, medications, and procedures) was collected at the 12 week visit.

Within trial assessments of health related quality of life (using the EQ5D) were also used in the economic analysis. EQ5D scores were used to weight lifetime lived by its quality; the EQ5D tariff developed for the UK was used to derive the scores from the participants responses to the EQ5D's descriptive system. The cost effectiveness analysis thus used QALY (Quality Adjusted Life Years) as the outcome measure.

Sample Size

The trial was originally designed with two co-primary outcomes: all-cause mortality by 14 days and bacteriological failure/recurrence or death by 12 weeks. Assuming 80% power, two-sided alpha 0.025 (to adjust for multiple testing given 2 co-primary outcomes), and a 10% loss to follow-up by 12 weeks, 920 participants were needed 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. Assuming 80% power, two-sided alpha 0.025, and a lower 4% loss to follow-up by 14 days (as most participants remained in hospital over this timescale), 940 participants were needed 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 was originally therefore 940 participants.

Recruitment to the trial was slower than anticipated. To facilitate successful completion of the trial and at the request of the trial funder, after 3 years recruitment 14-day mortality was moved from a co-primary to a secondary outcome. 12-week bacteriological failure/recurrence or death therefore became the sole primary outcome with consequent decrease in sample size (due to increase in the two-sided alpha (Type I error) from 0.025 (two co-primary outcomes) to 0.05 (one primary outcome)). With 12-week bacteriological failure/recurrence or death as the sole primary outcome, the total sample size became 770 participants (alpha=0.05, other assumptions as above).

The protocol and statistical analysis plan specified that the primary outcome (bacteriologically-confirmed failure/recurrence or death) would be analysed using time-to-event methods as described below. The sample size calculation treated this outcome as binary, in order to produce a conservative estimate of sample size given uncertainties in the underlying assumptions, and since all patients were to be followed for a fixed 12 week period (that is, no additional power was gained from longer follow-up in some patients).

Statistical Methods

Randomised groups were compared followed the principle of intention-to-treat including all follow-up regardless of changes to treatment. The Statistical Analysis Plan pre-specified that any patient who was randomised in error (defined as realising that the patient should not have been randomised before taking blinded study drug and not ever taking study drug) and hence not followed up would be excluded. The blinding means that there was no possibility that knowledge of randomised allocation affected this judgement about what was an error. Any participants who were randomised in good faith (i.e. not by mistake) but never took study drug were included in all analyses.

Time-to-event analyses measured time from randomisation. Analyses of clinical outcomes censored at the earliest of 12 weeks from randomisation and the last clinical information. Analyses of mortality censored at the earliest of the timescale being considered (2 weeks, 12 weeks) or last vital status information (including that ascertained at trial closure through the National Health Service records).

The primary analyses were unstratified because the randomisation stratification factor (centre) was expected to have some small strata and participants in these strata might then not contribute to comparisons. Results from secondary stratified analyses (stratified logrank test and stratified Cox regression) were very similar (data not shown). Lost-to-follow-up was defined as not having been assessed in person or by telephone within a [-1,+8] week window of the 12 week final visit by a trial clinician and not having information on whether or not signs/symptoms of *S. aureus* were present (e.g. from the patient's General Practitioner).

Primary analysis of the primary endpoint included all randomised participants other than those considered randomised in error (following the statistical analysis plan): secondary analysis of the primary endpoint was to exclude those (expected <1%) who were subsequently identified as having had a rifampicin resistant *S. aureus* bacteraemia on susceptibility testing. As no patients were identified after randomisation as having had a rifampicin resistant *S. aureus* bacteraemia at enrolment, this analysis was identical to the primary analysis. In the statistical analysis plan (but not the protocol), a per-protocol analysis was also specified for the primary

endpoint, including all participants in the primary intention-to-treat analysis who received active/placebo for ≥80% of days from start of trial drug to earliest of: 14 days subsequently/death/discontinuation of active antibiotics (not including trial drug).

Safety analyses included all data between randomisation and 12 weeks post-randomisation (inclusive). Non-fatal events related to S. aureus bacteraemia were not considered AEs/SAEs in the protocol.

Where composite outcomes did not include all-cause mortality as part of the composite, competing risks analysis methods were used. Analogous to a Kaplan-Meier estimate, competing risks methods use cumulative incidence functions to estimate the probability of the event. We estimated the effect of randomised group on the subdistribution hazard that corresponds to this cumulative incidence function. Stratification is not possible with the estimating equation approach used to estimate these subdistribution hazards and so these analyses were conducted unstratified.

CRP and liver function test results were compared between randomised groups over time using generalised estimating equations (GEE) (normal distribution, independent correlation structure) with randomised group, adjusting for the stratification factor, baseline values and scheduled visit week as categorical independent variables and interaction between baseline values and scheduled visit week. The closest measurement to each scheduled visit date within equally spaced windows was used as the measurement at each scheduled visit. The midpoint between two scheduled assessment days was taken as belonging to the latter window. Where there were two values within one of these equally spaced windows, but both equidistant from the nominal assessment day, the later value was used. Analyses were based on observed data. To account for CRP values above limit of quantification in one centre (that is, CRP only reported as >156 mg/L if above this threshold), mean CRP was estimated using normal interval regression. For analyses of change from baseline, these values were assumed equal to the limit of quantification.

For blood cultures, baseline (used to define baseline resistance/susceptibility) was defined as the closest up to and including day 0, and up to one day post-randomisation providing this was on or before date of start of trial drug. Cultures prior to randomisation were used in preference to cultures the same number of days after randomisation, but on or before the date of start of

trial drug. As eligibility was based on the screening positive blood culture, and because the intention was to characterise persisting bacteraemia, baseline bacteraemia included cultures on day-one where a culture on the day of or on the day prior to randomisation was not available. For duration of bacteraemia, baseline was defined as the closest up to and including day 0 within the preceding day, and up to one day post-randomisation.

For laboratory measurements (e.g. CRP), baseline was defined as the closest up to and including day 0 within the preceding 4 days, and up to one day post-randomisation providing this was on or before date of start of trial drug. Measurements prior to randomisation were used in preference to measurements the same number of days after randomisation, but on or before the date of start of trial drug.

A deep infection focus was defined as infection of implanted vascular device, native/prosthetic heart value, native/prosthetic bone/joint, or deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection).

Information on all antibiotics received through 12 weeks was collected, but not according to specific indication. Primary antibiotic treatment, and its duration, was therefore defined by complete cessation of all antibiotics for 2 days, with the exception of vancomycin where intermittent dosing up to 1 week was allowed. The cessation of vancomycin was defined by adding the number of days between the last two doses to the date of the final dose.

SUBGROUP ANALYSES

Subgroup analyses were conducted to assess consistency of effects across different participant characteristics. The primary method of assessing subgroup effects was an interaction test within a Cox proportional hazards regression. For the continuous factors we used both categorisation and natural cubic splines (five knots at the 10th, 25th, 50th, 75th, and 90th centiles; four knots at the 10th, 33rd, 67th, and 90th centiles for Charlson comorbidity index score (as 10th and 25th centiles identical)) to test for interactions. Subgroup analyses were conducted unstratified to avoid losing information from small strata with no events in one randomised group. No formal adjustment for multiple testing was made for subgroup analyses.

We pre-specified in the protocol twelve subgroup analyses for the primary endpoint; namely 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 trial drug only or regimen containing IV trial 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, age and CRP (terciles).

The statistical analysis plan included 6 additional subgroup analyses, but prioritised the subgroup analyses as follows (*=in protocol).

1. *Time from initiation of first active antibiotic treatment to initiation of randomised treatment (0-24, >24-48, >48-72, >72 hours)
1. *Class of initial antibiotic treatment, and according to individual drugs where these are used by >10% of the trial population
1. *MRSA/MSSA
1. *IV catheter (central/peripheral venous line)/implanted vascular device-associated infection vs other (based on portal of entry)
1. *Deep focus (implanted vascular device, native/prosthetic heart valve, native/prosthetic joint, deep tissue infection/abscess)/no deep focus (based on foci of infection)
1. *Endocarditis (main focus/foci of infection at time first positive blood culture taken = native heart valve/prosthetic heart valve)/no endocarditis
1. *Foci of infection known/not known
1. *Age (terciles)
2. *Initial oral randomised treatment frequency (once vs twice daily)
2. *Initial treatment with oral trial drug only or regimen containing IV trial drug
2. *Whether gentamicin was administered between first positive blood culture and 48 hours post-randomisation, regardless of activity
2. Whether any active antibiotic other than that first administered (excluding trial drug), trial drug and gentamicin was administered between first positive blood culture and 48 hours post-randomisation (yes vs no)
2. *Baseline CRP (terciles)
2. Charlson comorbidity index score (0, 1-2, 3-4, ≥5)
3. Time from randomisation to initiation of randomised treatment (0-4, >4-12, >12-24, >24 hours)

3. Community, healthcare associated and nosocomial acquisition
3. Calendar year of randomisation
3. Baseline neutrophils (terciles)

We also considered additional exploratory subgroups defined by initial total daily dose (600 vs 900 mg), and whether or not the patient was bacteraemic at randomisation, leading to 20 subgroups in total.

Data Collection and Handling

Data was entered by staff at each NHS Trust Hospital on to eCRFs on the online ARREST trial database. Staff with data entry responsibilities were required to complete database training before they were granted access to the database. Data was exported into Stata (v14.2) (StataCorp LP, College Station, TX, USA) for analysis.

Interim Analyses

The trial was reviewed by the ARREST Data Monitoring Committee (DMC). They met four times in strict confidence over the course of the trial: 14 November 2013, 31 October 2014, 26 May 2015, 24 February 2016. DMC reccommendations were communicated through a letter to the TSC following each meeting.

Clinical Site Monitoring

Trial monitoring was carried out according to the protocol. Trial centres agreed to provide access to source data and consent was gained from patients for direct access to patient notes. All centres that had a minimum of 4 patients that had completed follow-up (week 12 visit or death) were monitored on-site at least once during the trial. The following data were validated from source documents:

- eligibility and signed consent
- trial drug and antibiotic management

- safety events
- any data concerns raised by central monitoring

Patient and Public Involvement

The ARREST trial was developed with the Healthcare-associated Infection Service Users Research Forum (SURF: www.hcaisurf.org); in particular Jennifer Bostock who was the Patient and Public Involvement (PPI) representative on the ARREST Trial Steering Committee. Ms Bostock advised on the inclusion of incapacitated adults, the application of the Mental Capacity Act, and on the information provided to patients. SURF is no longer active, but Ms Bostock is helping disseminate the trial's results beyond the academic and healthcare professional community to other patient groups that she works with including MRSA Action UK.

In particular, given recruitment challenges, Ms Bostock developed and led the sub-study investigating patients' and carers' reasons for and for not participating in the trial. This is reported in full in Chapter 4 Trial Participation Qualitative Sub-study.

Protocol Changes

The trial was approved by the London (Westminster) Research Ethics Committee (12/LO/0637). See **Appendix 1** for changes to the protocol.

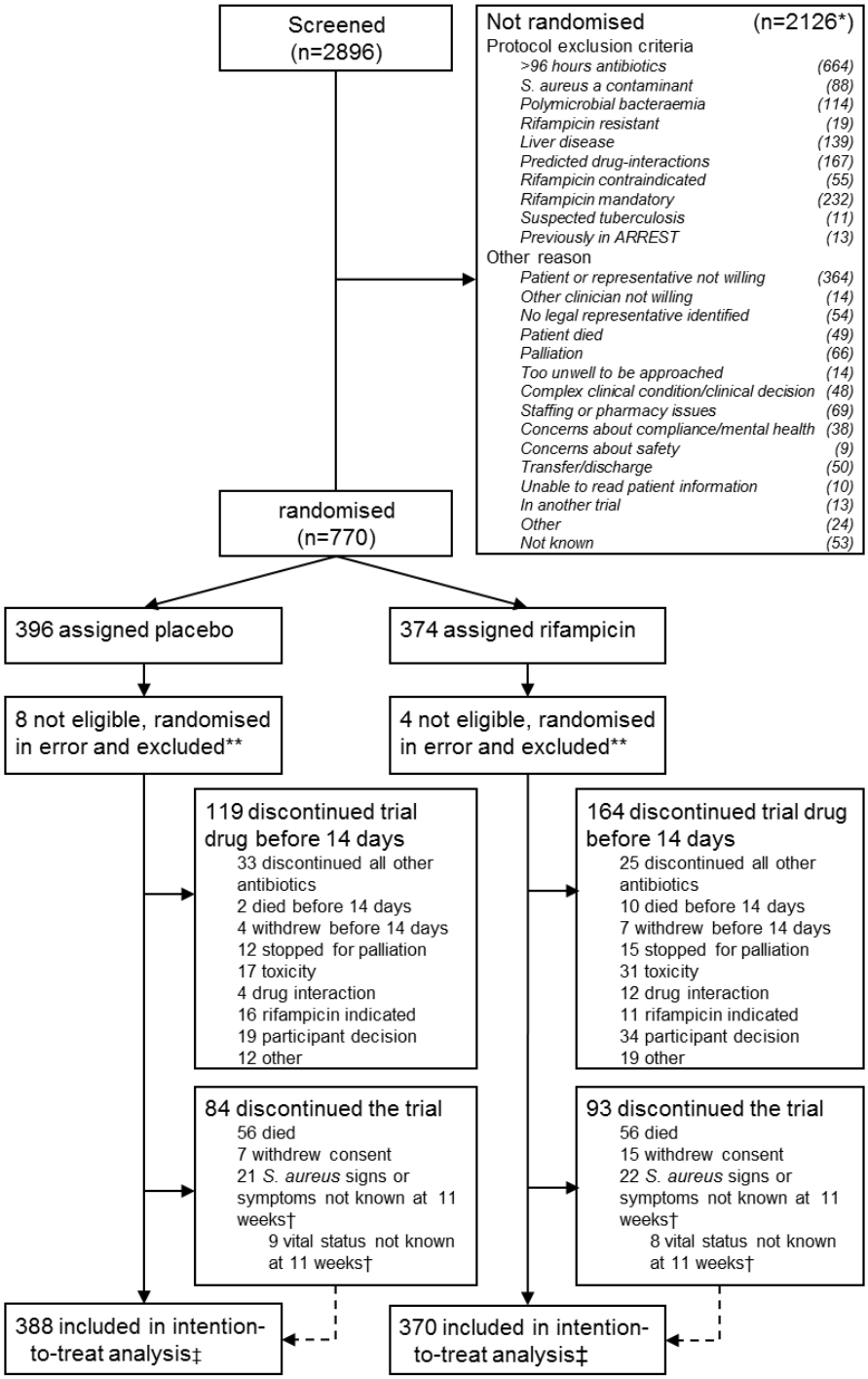
Chapter 3 Results

Participant flow diagram

Between 10th December 2012 and 25th October 2016, 770 participants from 29 United Kingdom hospital groups were randomised to add placebo (n=396) or rifampicin (n=374) to their 'backbone' antibiotic treatment (**Figure 2**). 2896 were screened for entry to the trial. The most common reason for not randomising a potentially eligible participant was that they had already received >96 hours of antibiotics (n=664). In 364 cases the participant was not willing. Rifampicin was considered mandatory in 232 cases. Known rifampicin resistance occurred in only 19 cases. However 139 cases were not eligible because of pre-existing liver disease raising concerns about rifampicin treatment and 167 cases because of predicted drug interactions.

12 (8 placebo; 4 rifampicin) were randomised in error (the participant should not have been randomised and never received trial drug) and were excluded following the Statistical Analysis Plan. Of these 12 participants, seven participants had predicted drug-interactions, two were misdiagnosed (*S. aureus* was not grown from blood), rifampicin was considered mandatory in one patient, one other clinician considered that the participant should not have been randomised due to acute kidney injury, one other clinician considered participant should not have been randomised as they were in another study (not of an investigational medicinal product, allowed according to the protocol).

Thus 758 (388 placebo, 370 rifampicin) participants were included in the analyses. The median (IQR) [range] number of patients recruited per centre was 11 (4-30) [1-163]. 415 (54.7%) participants were recruited from five centres (Oxford n=163, Guy's and St Thomas's n=99, Liverpool n=62, Plymouth n=48 and Sheffield n=43). The large number of centres recruiting small numbers of participants together with the relatively large block size (6-8) led to a small imbalance in the numbers included randomised to placebo (n=388) and rifampicin (n=370).



* reasons are not mutually exclusive, therefore total is more than the number of participants not randomised

** 7 participants with predicted drug-interaction, 2 misdiagnosed (*S. aureus* not grown from blood but only other samples), rifampicin considered mandatory in 1, 1 other clinician considered participant should not have been randomised due to acute kidney injury, 1 other clinician considered participant should not have been randomised as they were in another study (not of an investigational medicinal product)

† Final 12 week visit could occur any time from 11 weeks onwards according to the protocol. Consent withdrawals not included in these numbers

‡ Time-to-event analyses included all time at risk from randomisation to the earliest of the event or last clinical follow-up if the event had not occurred.

Figure 2: Participant flow diagram

Baseline characteristics

Baseline characteristics were well-balanced between randomised groups (**Table 1, Table 2**).

495 (65.3%) participants were men (**Table 1**). They were aged median (interquartile range (IQR)) 65 (50-76) years, weighed 76.0 kg (64.0-90.0) and had median Charlson co-morbidity score 2 (0-3). Diabetes (30.1%), renal disease (18.2%), cancer (16.6%) and chronic lung disease (11.9%) were all common co-morbidities. 83 (10.9%) were active injecting drug users. 70 (9.2%) participants were in an intensive care unit, and 90 (11.9%) had had surgery in the last 30 days. 127 (16.8%) had consent provided by a legal representative due to incapacity. Reflecting disease severity, mean (Standard Error) CRP was 164 (3.7) mg/L and median (IQR) Sequential Organ Failure Assessment (SOFA) score was 2 (1-4).

At randomisation, participants had already received a median (IQR) 62 (42-75) hours of active antibiotics, with their first blood culture taken a median (IQR) 3 (2-3) days previously and their first symptoms occurring a median (IQR) 4 (3-6) days previously. 157/642 (24.5%) still had a positive blood culture on the day of randomisation.

485 (64.0%) infections were community-acquired, with only 132 (17.4%) nosocomial; 47 (6.2%) were caused by methicillin-resistant *S. aureus* (MRSA). No patients were known to have rifampicin-resistant *S. aureus* bacteraemia at randomisation.

The initial focus was deep in 301 (39.7%), including 33 (4.4%) with endocarditis and 14 (1.8%) with infected prostheses; 130 (17.2%) were due to infected central/peripheral lines; 138 (18.2%) associated with skin/soft tissue infections; another type of focus was identified in 49 (6.5%) and not established in 139 (18.3%).

In 255 (33.6%) participants the most likely portal of entry of *S. aureus* into the bloodstream was a clinically apparent skin or soft tissue infection unrelated to a surgical intervention. Central or peripheral lines were the most likely portal of entry in 141 (18.6%) participants, although 191 (25.7%) had a vascular catheter in situ at randomisation. For 218 (18.6%) participants the portal of entry was unknown.

Table 1 Participant characteristics at randomisation

Factor	Placebo N=388	Rifampicin N=370*	Total N=758*
Male	246 (63.4%)	249 (67.3%)	495 (65.3%)
Age at last birthday (years)	66 (51, 76)	64 (49, 76)	65 (50, 76)
Charlson comorbidity score*	2 (0, 3)	1 (0, 3)	2 (0, 3)
Cancer (N=756)	60 (15.5%)	66 (17.8%)	126 (16.6%)
Chronic lung disease (N=756)	42 (10.8%)	48 (13.0%)	90 (11.9%)
Congestive heart disease (N=756)	40 (10.3%)	42 (11.4%)	82 (10.8%)
Moderate or severe liver disease (N=755)	5 (1.3%)	5 (1.4%)	10 (1.3%)
Moderate or severe renal disease (N=755)	80 (20.6%)	58 (15.7%)	138 (18.2%)
Diabetes*	119 (30.7%)	109 (29.5%)	228 (30.1%)
Active injecting drug use (N=751)	41 (10.6%)	42 (11.4%)	83 (10.9%)
Weight (N=755)	76.0 (65.0, 90.0)	76.0 (64.0, 89.0)	76.0 (64.0, 90.0)
Admitted to ICU *	36 (9.3%)	34 (9.2%)	70 (9.2%)
CRP (mg/L) (N=755) **	163 (5.2)	166 (5.3)	164 (3.7)
White cell count (10^9/L) (N=752)	9.5 (6.7, 13.4)	9.5 (7.1, 13.1)	9.5 (6.9, 13.2)
Neutrophil count (10^9/L) (N=752)	7.3 (4.7, 11.0)	7.4 (4.9, 10.7)	7.3 (4.8, 10.9)
Lymphocyte count (10^9/L) (N=751)	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)
SOFA score*	2 (1, 4)	2 (1, 4)	2 (1, 4)
Vascular catheter in situ (N=744)	102 (26.8%)	89 (24.5%)	191 (25.7%)
Surgery in the last 30 days (N=756)	53 (13.7%)	37 (10.1%)	90 (11.9%)
Days between first new symptom caused by *S. aureus* and randomisation and randomisation*	4 (3, 6)	4 (3, 6)	4 (3, 6)
Days between drawing of first positive blood culture and randomisation*	3 (2, 3)	3 (2, 4)	3 (2, 3)
Hours of active antibiotic therapy before randomisation	63 (42, 75)	60 (41, 76)	62 (42, 75)
Blood culture positive at randomisation	69/326 (21.2%)	88/316 (27.8%)	157/642 (24.5%)

* One rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant. If any other participants had missing data, then denominators are shown.
** Mean (SE) estimated using normal interval regression to account for values above limit of quantification in one centre.
Note: showing n(%) for categorical factors, or median (IQR) for continuous factors other than CRP where mean(SE) is shown.

Table 2 Infection characteristics at randomisation

Factor	Placebo N=388	Rifampicin N=370*	Total N=758*
Mode of acquisition of infection*			
Community acquired	240 (61.9%)	245 (66.2%)	485 (64.0%)
Nosocomial infection (onset ≥48 hrs after admission)	76 (19.6%)	56 (15.1%)	132 (17.4%)
Healthcare associated (all other)	72 (18.6%)	68 (18.4%)	140 (18.5%)
MRSA	21 (5.4%)	26 (7.0%)	47 (6.2%)
Rifampicin-resistant infection at randomisation (N=750) ††	0	0	0
Main focus/foci of infection *†			
Native heart valve	16 (4.1%)	17 (4.6%)	33 (4.4%)
Native joint	34 (8.8%)	29 (7.8%)	63 (8.3%)
Prosthetic heart valve/joint **	5 (1.3%)	9 (2.4%)	14 (1.8%)
Implanted vascular device (other than intravenous catheter)	23 (5.9%)	13 (3.5%)	36 (4.7%)
Deep tissue infection/abscess	94 (24.2%)	82 (22.2%)	176 (23.2%)
Central or peripheral intravenous catheter	67 (17.3%)	63 (17.0%)	130 (17.2%)
Skin/soft tissue (excluding wounds)	66 (17.0%)	72 (19.5%)	138 (18.2%)
Surgical wound	15 (3.9%)	10 (2.7%)	25 (3.3%)
Pneumonia or urinary tract infection	30 (7.7%)	30 (8.1%)	60 (7.9%)
Not established	67 (17.3%)	72 (19.5%)	139 (18.3%)
Any deep-seated focus ‡	159 (41.0%)	142 (38.4%)	301 (39.7%)
Likely portal of entry of *S. aureus* into the bloodstream†			
Clinically apparent skin or soft tissue infection unrelated to a surgical intervention	131 (33.8%)	124 (33.5%)	255 (33.6%)
Infected surgical wound within last 3 months, with or without associated prosthesis	19 (4.9%)	19 (5.1%)	38 (5.0%)
Peripheral vascular catheter (including arterial line)	23 (5.9%)	26 (7.0%)	49 (6.5%)
Central vascular catheter (including PICC line)	50 (12.9%)	42 (11.4%)	92 (12.1%)
Other implanted vascular device (e.g. pacemaker, stent, graft)	15 (3.9%)	12 (3.2%)	27 (3.6%)
Respiratory	16 (4.1%)	13 (3.5%)	29 (3.8%)
Per-urethral or supra-pubic urinary catheter	7 (1.8%)	8 (2.2%)	15 (2.0%)
Recent (within 1 week of bacteraemia) urological surgery	1 (0.3%)	3 (0.8%)	4 (0.5%)
Not known (absence of any of the above)	110 (28.4%)	108 (29.2%)	218 (28.8%)
Injecting drug user	8 (2.1%)	9 (2.4%)	17 (2.2%)
Corticosteroid Injection Into Joint	4 (1.0%)	2 (0.5%)	6 (0.8%)
Other	2 (0.5%)	3 (0.8%)	5 (0.7%)
Not completed (missing data)	2 (0.5%)	1 (0.3%)	3 (0.4%)

* One rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant.
† Individuals could have multiple foci, and portal of entry,, so sum is more than total randomised
** 2 placebo, 5 rifampicin with prosthetic heart valves; 3 placebo, 4 rifampicin with prosthetic joints.
‡ Infection of implanted vascular device, native/prosthetic heart value, native/prosthetic bone/joint, deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection).
†† Not required to be known at the point of randomisation for eligibility.
Note: showing n(%) for categorical factors, or median (IQR) for continuous factors.

Follow-up and treatment received

Overall completeness of scheduled visits was high up to 14 days. Excluding visits after death or discharge, day-3 visits were missed in 10/372 (2.7%) placebo versus 12/350 (3.4%) rifampicin participants, day-7 visits were missed in 15/337 (4.5%) placebo versus 16/311 (5.1%) rifampicin participants, day-10 visits were missed in 22/293 (7.5%) placebo versus 26/262 (9.9%) rifampicin participants, and day-14 visits were missed in 9/230 (3.9%) placebo versus 13/204 (6.4%) rifampicin participants. Completeness dropped after 14 days when patients started to be discharged, for example visits were missed in 21/149 (14.1%) placebo versus 19/134 (14.2%) rifampicin participants at day-21; 23/115 (20.0%) placebo versus 23/93 (24.7%) rifampicin participants at day-28; and 25/89 (28.1%) placebo versus 19/58 (32.8%) rifampicin participants at day-35.

22 (2.9%) participants withdrew consent. At the 12-week visit, only 39 (5.1%) had unknown vital status and 65 (8.6%) were not assessed for signs/symptoms of *S. aureus* infection (including consent withdrawals).

23 (3.0%) participants were still in hospital at 12-weeks (15 (3.9%) placebo versus 8 (2.2%) rifampicin, p=0.17). The median (IQR) initial hospitalisation duration was 21 (14-50) versus 22 (13-43) days in placebo and rifampicin groups respectively (p=0.80) (**Figure 3**). 132 (39.8%) placebo versus 138 (44.8%) rifampicin participants were discharged on outpatient parental therapy (p=0.35). 94 (24.2%) placebo versus 83 (22.4%) rifampicin participants were re-admitted post-discharge and before 12-weeks (p=0.56), spending a median (IQR) 9 (4-20) and 10 (3-20) nights in hospital post-original-discharge respectively. Any admission was considered for reasons relating to *S. aureus* bacteraemia in 16 (4.1%) placebo and 9 (2.4%) rifampicin participants (p=0.19).

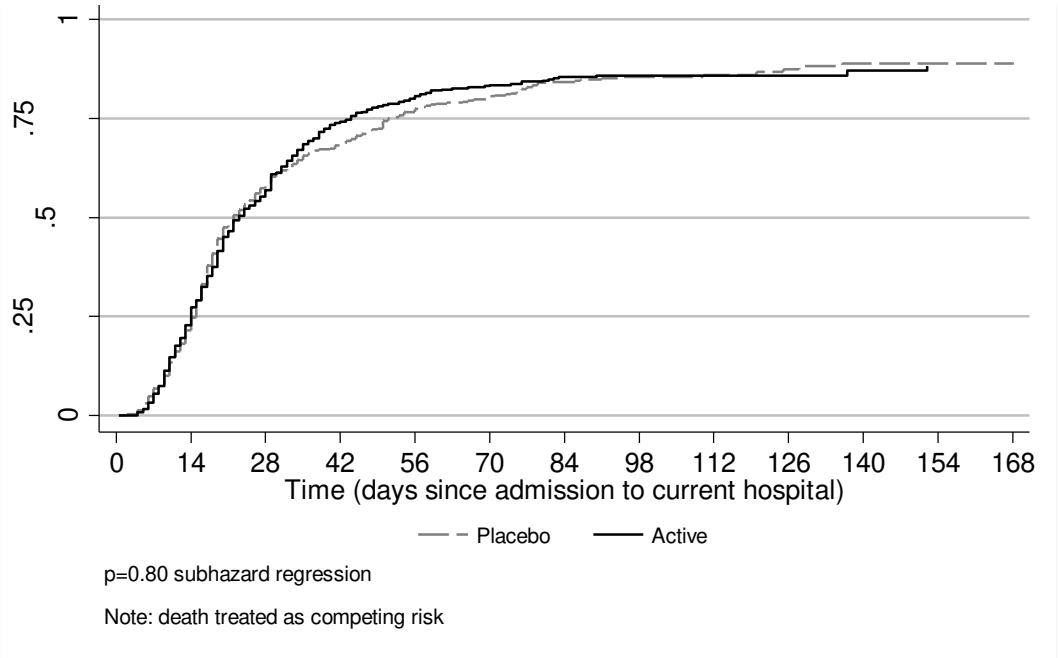


Figure 3 Days from admission to current hospital and original post-randomisation discharge

744 (98.2%) participants initiated blinded trial drug, a median (IQR) 4.3 (2.3-7.8) hours after randomisation. Reasons for not initiating blinded trial drug were patient decision (n=7); increasing liver enzyme levels (2); started on open-label rifampicin (2); withdrawn for palliation (1); incorrectly believed that the bacteraemia was rifampicin resistant (1); and unable to access IV trial drug from trials pharmacy at weekend (1).

96 (12.7%) initiated IV trial drug rather than oral trial drug (

Table 3). 595 (78.5%) initiated 900mg daily rather than 600 mg daily and 362 (52.2%) twice-daily rather than once-daily. The median (IQR) dose was 11.1 (10.0-12.9) mg/kg. Trial drug was initiated a median (IQR) 68 (48-85) hours after starting active antibiotics for the current infection. Trial drug was continued for median (IQR) 12.6 (6.0-13.2) days in rifampicin participants versus 13.0 (11.3-13.5) days in placebo participants ($p<0.0001$; primarily due to antibiotic-modifying AEs and drug-drug interactions, see below). 60 (15.5%) placebo versus 51 (15.6%) rifampicin participants ever received IV trial drug. Percentages reporting missing any doses of trial drug ranged from 9.5%-16.2% but did not differ between randomised groups (**Figure 4**; global $p=0.71$).

Table 3 Trial drug treatment

Factor	Placebo N=388	Rifampicin N=370	**Total N=758**
Never initiated trial drug	8 (2.1%)	6 (1.6%)	14 (1.8%)
Initiated IV trial drug	51 (13.1%)	45 (12.2%)	96 (12.7%)
Initiated oral trial drug	329 (84.8%)	319 (86.2%)	648 (85.5%)
Initiated trial drug once-daily	175 (45.1%)	173 (46.8%)	348 (45.9%)
Initiated trial drug twice-daily	205 (52.8%)	191 (51.6%)	396 (52.2%)
Initiated trial drug 600mg daily	74 (19.1%)	75 (20.3%)	149 (19.7%)
Initiated trial drug 900mg daily	306 (78.9%)	289 (78.1%)	595 (78.5%)
Initial total daily dose (mg/kg) (N=741)	11.2 (9.9, 12.9)	11.0 (10.0, 12.7)	11.1 (10.0, 12.9)
Hours from starting active antibiotics to starting trial drug	69 (49, 85)	68 (46, 85)	68 (48, 85)
Hours from randomisation to initiation of randomised treatment	4.2 (2.3, 7.6)	4.3 (2.3, 8.0)	4.3 (2.3, 7.8)
Days on trial drug	13.0 (11.3, 13.5)	12.6 (6.0, 13.2)	12.8 (7.9, 13.4)
Total duration of study drug (days)			
0	8 (2.1%)	6 (1.6%)	14 (1.8%)
<3	18 (4.6%)	22 (5.9%)	40 (5.3%)
3-5	28 (7.2%)	57 (15.4%)	85 (11.2%)
6-9	24 (6.2%)	43 (11.6%)	67 (8.8%)
10-13	49 (12.6%)	42 (11.4%)	91 (12.0%)
14	255 (65.7%)	197 (53.2%)	452 (59.6%)
>14	6 (1.5%)	3 (0.8%)	9 (1.2%)
Ever received IV trial drug	60 (15.5%)	56 (15.1%)	116 (15.3%)

Note: showing n(%) or median (IQR).

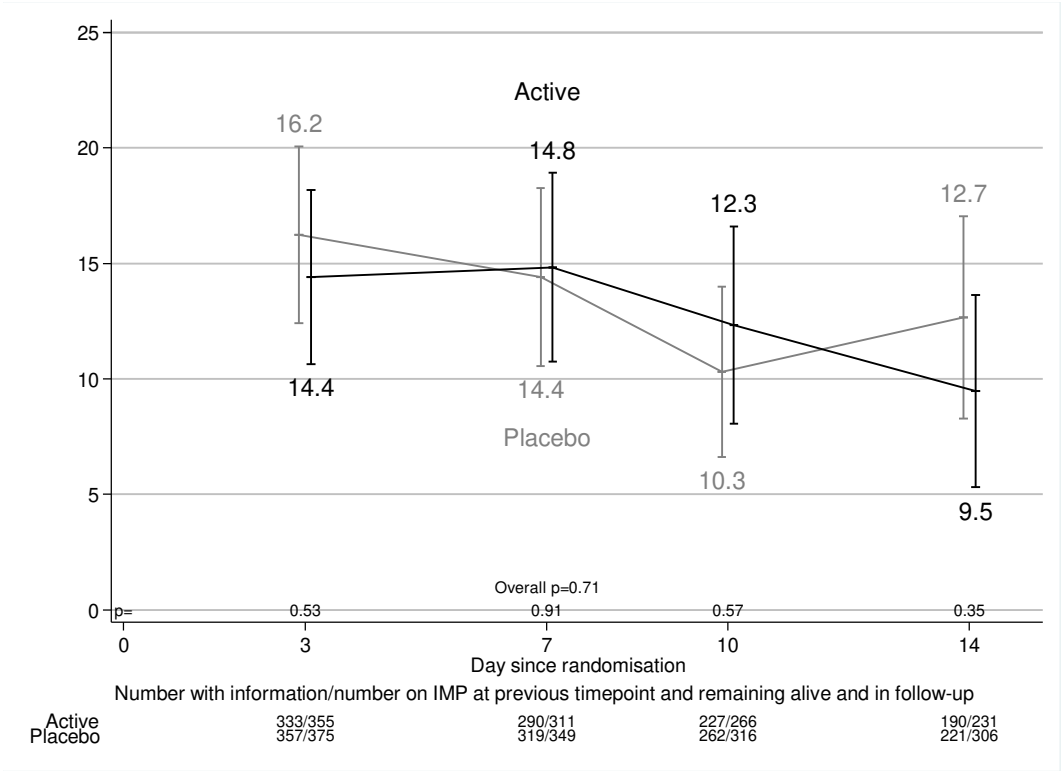


Figure 4 Percentage reporting missing one or more doses of trial drugs since the previous scheduled visit

A substantial variety of 'backbone' active antibiotics were used (**Table 4;** details in **Table 26** in **Appendix 2**). Flucloxacillin was given in 619 (81.7%) participants, and vancomycin or teicoplanin in 380 (50.1%) participants at some point in the primary treatment course, with no evidence of difference between randomised groups (p=0.44 and p=0.34, respectively). Stat (one-off) doses of gentamicin or amikacin were used in 199 (26.3%) participants (p=0.89). There was no evidence that the numbers of antibiotics used (median (IQR) 3 (2-4)) or the total duration of active anti-staphylococcal treatment (including therapy received before randomisation) (median (IQR) 29 (18-45) days) differed between groups (p=0.98 and 0.64 respectively) (**Table 4**). Post-randomisation active anti-staphylococcal treatment was taken for median (IQR) 27 (15-41) days in placebo vs 26 (15-43) days in rifampicin participants.

32 (8.6%) rifampicin participants versus 52 (13.4%) placebo participants used open-label rifampicin at some point after randomisation (p=0.04). Median time from randomisation to initiation of open-label rifampicin was 14 days (IQR 7-18) (**Table 4**). There was a trend to slightly fewer participants initiating open-label rifampicin from 14 days onwards (i.e. after stopping trial drug; 14 (3.8%) vs 27 (7.0%) placebo, p=0.053). Open-label rifampicin was used in participants with a range of original infection foci (**Table 5**). The median (IQR) duration of open-label rifampicin was 25 days (13-45) in placebo vs 32 (26-48) in rifampicin participants.

60 (15.5%) placebo participants received antibiotics after the primary course versus 34 (9.2%) rifampicin participants (p=0.01).

Table 4 'Backbone' antibiotic treatment

Factor	Placebo N=388	Rifampicin N=370	**Total N=758**
'Backbone' active antibiotic treatment*			
Flucloxacillin	321 (82.7%)	298 (80.5%)	619 (81.7%)
Co-amoxiclavulante	122 (31.4%)	107 (28.9%)	229 (30.2%)
Piperacillin/tazobactam	115 (29.6%)	102 (27.6%)	217 (28.6%)
Vancomycin/teicoplanin	188 (48.5%)	192 (51.9%)	380 (50.1%)
Cephalosporin	110 (28.4%)	104 (28.1%)	214 (28.2%)
Fluoroquinolone	47 (12.1%)	46 (12.4%)	93 (12.3%)
Macrolide	30 (7.7%)	28 (7.6%)	58 (7.7%)
Clindamycin	23 (5.9%)	36 (9.7%)	59 (7.8%)
Tetracycline	29 (7.5%)	26 (7.0%)	55 (7.3%)
Gentamicin/amikacin	101 (26.0%)	98 (26.5%)	199 (26.3%)
Stat gentamicin/amikacin	95 (24.5%)	87 (23.5%)	182 (24.0%)
Carbapenem	38 (9.8%)	35 (9.5%)	73 (9.6%)
Other antibiotic**	52 (13.4%)	52 (14.1%)	104 (13.7%)
Number of antibiotics received during *S. aureus* infection episode (excluding study drug)	3 (2, 4)	3 (2, 4)	3 (2, 4)
Days of antibiotic treatment for *S. aureus* infection episode (days)	30 (18-44)	29 (17-45)	29 (18-45)
Rifampicin used open-label	52 (13.4%)	32 (8.6%)	84 (11.1%)
Initiated <14 days from randomisation†	25 (6.4%)	18 (4.9%)	43 (5.7%)
Initiated ≥14 days from randomisation	27 (7.0%)	14 (3.8%)	41 (5.4%)

* including active antibiotics taken from the first blood culture sample throughout the illness episode
** excluding open-label rifampicin
† that is, blinded trial drug stopped and open-label rifampicin initiated for clinical reasons.
Note: showing n(%) or median (IQR).

Table 5 Initial infection focus in participants who received open-label rifampicin at any point during 12 weeks follow-up

Infection focus	Placebo N=52	Rifampicin N=32	Total N=84
Central venous line (including picc line)	1 (1.9%)	2 (6.3%)	3 (3.6%)
Implanted vascular device (e.g. pacemaker, stent, graft)	8 (15.4%)	0 (0.0%)	8 (9.5%)
Infected intravascular thrombus	2 (3.8%)	3 (9.4%)	5 (6.0%)
Native heart valve	6 (11.5%)	2 (6.3%)	8 (9.5%)
Prosthetic heart valve	1 (1.9%)	2 (6.3%)	3 (3.6%)
Native joint	1 (1.9%)	5 (15.6%)	6 (7.1%)
Prosthetic joint	0 (0.0%)	1 (3.1%)	1 (1.2%)
Vertebral bone/disc	13 (25.0%)	8 (25.0%)	21 (25.0%)
Epidural or intraspinal empyema	4 (7.7%)	1 (3.1%)	5 (6.0%)
Deep tissue infection or abscess	6 (11.5%)	3 (9.4%)	9 (10.7%)
Surgical wound	3 (5.8%)	0 (0.0%)	3 (3.6%)
Skin/Soft tissue (excluding wounds)	6 (11.5%)	3 (9.4%)	9 (10.7%)
Pneumonia	2 (3.8%)	1 (3.1%)	3 (3.6%)
Other ‡	6 (11.5%)	0 (0.0%)	6 (7.1%)
Not established	6 (11.5%)	9 (28.1%)	15 (17.9%)

‡ Central nervous system (n=2, both placebo); osteomyelitis (n=1, placebo); Urinary tract (n=3, all placebo)

159 placebo versus 142 rifampicin participants had a deep focus which was drained/removed in 35 (22.0%) versus 29 (20.4%), a median (IQR) 5 (2-12) and 3 (1-6) days from randomisation respectively (**Table 6**). 88 placebo versus 76 rifampicin participants had an intra-vascular device which was removed in 62 (70.5%) versus 60 (78.9%), a median (IQR) 2 (0-3) and 1 (0-2) days prior to randomisation respectively.

Table 6 Infection focus management

Factor	Placebo N=388	Rifampicin N=370	Total N=758
Any deep-seated focus *	159	142	301
Drained/removed	35 (22.0%)	29 (20.4%)	64 (21.3%)
Median days from randomisation to drainage/removal (IQR)	5 (2, 12)	3 (1, 6)	4 (2, 10)
Not removed	118 (74.2%)	109 (76.8%)	227 (75.4%)
Not known	6 (3.8%)	4 (2.8%)	10 (3.3%)
Non-device related focus	233	222	455
Drained/removed	39 (16.7%)	36 (16.2%)	75 (16.5%)
Median days from randomisation to drainage/removal (IQR)	4 (2, 11)	4 (2, 8)	4 (2, 10)
Not removed	187 (80.3%)	179 (80.6%)	366 (80.4%)
Not known	7 (3.0%)	7 (3.2%)	14 (3.1%)
Intra-vascular device	88	76	164
Removed	62 (70.5%)	60 (78.9%)	122 (74.4%)
Median days from randomisation to removal (IQR)	-2 (-3, 0)	-1 (-2, 0)	-1 (-2, 0)
Not removed	25 (28.4%)	15 (19.7%)	40 (24.4%)
Not known	1 (1.1%)	1 (1.3%)	2 (1.2%)
Non-vascular prosthetic implant/device	5	9	14
Removed	0 (0.0%)	2 (22.2%)	2 (14.3%)
Median days from randomisation to removal (IQR)	-	7 (2, 11)	7 (2, 11)
Not removed	5 (100.0%)	7 (77.8%)	12 (85.7%)

* Infection of implanted vascular device, native/prosthetic heart value, native/prosthetic bone/joint, deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection).

UNBLINDING AND BLINDING ASSESSMENT

At least one individual was unblinded for 14 participants (9 rifampicin, 5 placebo). In two cases this was only of a non-trial physician and ward pharmacist respectively, for participant safety. In three further cases this was of the research nurse only, but no other members of the clinical or research teams.

At the final 12 week visit, physicians and participants were asked which treatment they believed they had received. 203/243 (83.5%) physicians of participants randomised to rifampicin reported that they genuinely had no idea versus 249/279 (89.2%) placebo (p=0.08).

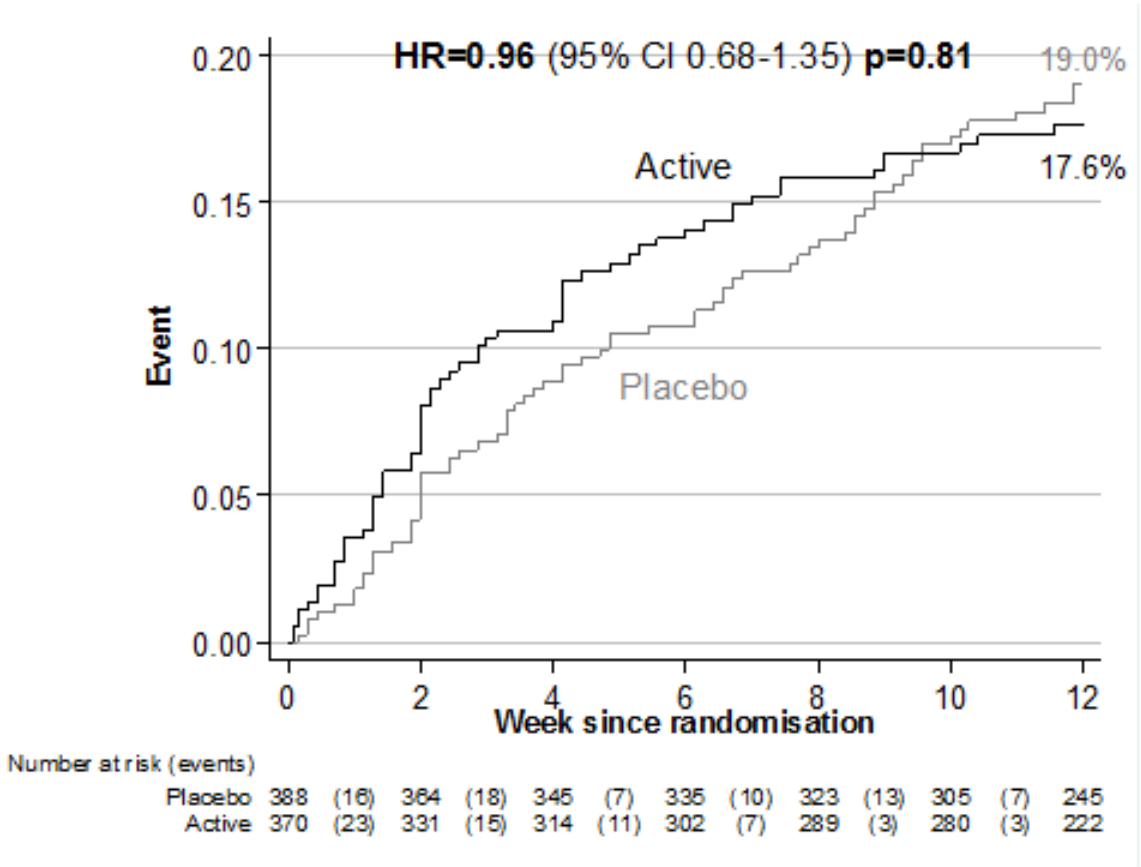
32 (13.2%) and 17 (6.1%) respectively guessed the correct allocation. In contrast, 113/199 (56.8%) participants randomised to rifampicin reported that they genuinely had no idea versus 159/229 (69.4%) placebo (p=0.007). 72 (36.2%) and 35 (15.3%) respectively guessed the correct allocation.

Primary endpoint

By 12-weeks, bacteriological failure/recurrence or death occurred in 62 (16.8%) rifampicin versus 71 (18.3%) placebo participants (absolute risk difference (RD) = -1.4% (95% CI -7.0%, +4.3%); hazard ratio (HR) = 0.96 (0.68-1.35) p=0.81, **Figure 5A**). In exploratory post-hoc analyses, comparing rifampicin with placebo there were 4 (1.1%) versus 5 (1.3%) failures (competing-risks p=0.82), 3 (0.8%) versus 16 (4.1%) recurrences (competing-risks p=0.01), and 55 (14.9%) versus 50 (12.9%) deaths without bacteriological failure/recurrence respectively (competing-risks p=0.30) (**Table 7**). The number-needed-to-treat to prevent one bacteriologically-confirmed recurrence was 29.

242 (65.4%) rifampicin versus 290 (74.7%) placebo were included in the per-protocol population (received active rifampicin/placebo for ≥80% of days from start of trial drug to earliest of: 14 days subsequently/death/discontinuation of active antibiotics (not including trial drug)). By 12 weeks, 39 (16.1%) rifampicin versus 49 (16.9%) placebo experienced bacteriological failure/recurrence or died (absolute risk difference (RD) = -0.8% (95% CI –7.3, +5.6); hazard ratio (HR) = 1.00 (0.65-1.52) p=0.99). An exploratory post-hoc analysis was also done additionally excluding participants in either group who started open-label rifampicin at any time during follow-up. 225 (60.1%) rifampicin versus 262 (67.5%) placebo were included in this post-hoc per-protocol population. By 12 weeks, 37 (16.4%) rifampicin versus 37 (14.1%) placebo experienced bacteriological failure/recurrence or died (absolute risk difference (RD) = +2.3% (95% CI –4.3, +8.8); hazard ratio (HR) =1.23 (0.78-1.93) p=0.38).

Of 28 failures/recurrences where *S. aureus* was isolated from a sterile site, paired baseline and failure/recurrence isolates were stored for 11 (39%). All failure/recurrence isolates were whole genome sequenced and within 12 single nucleotide variants of the baseline isolate (median 1 (IQR 1-6) (range 0-12)).



(b) Three priority subgroup analyses

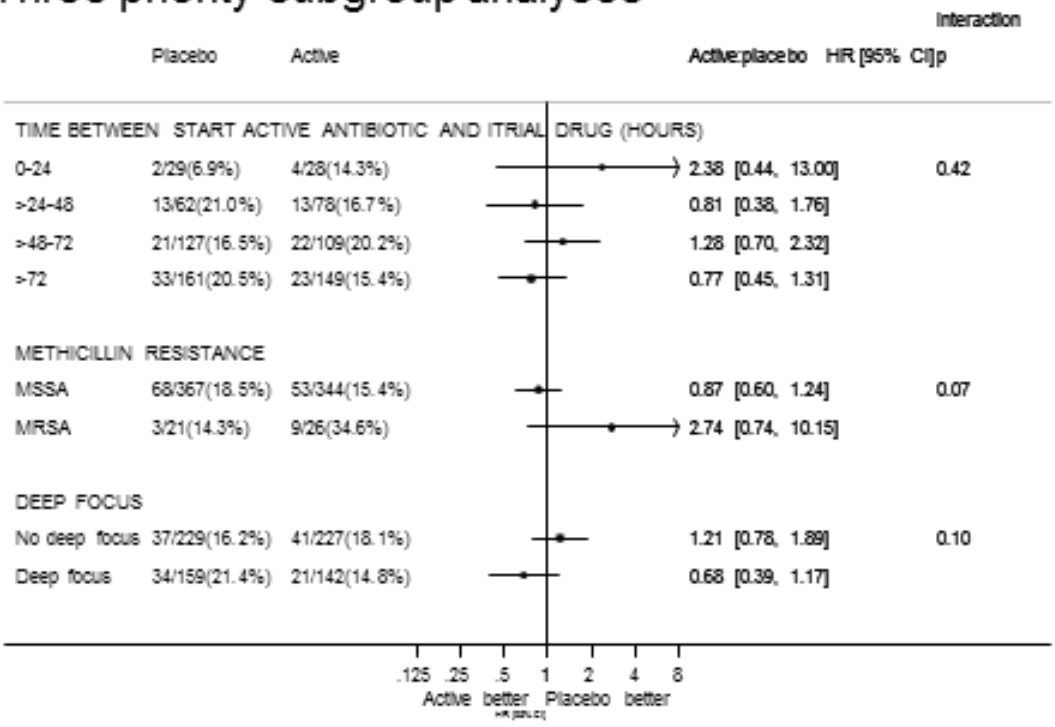


Figure 5 Bacteriological failure/recurrence or death (A) overall (B) according to three priority subgroups

Note: see **Figure 6** and **Figure 7** for other subgroup analyses.

Table 7 Failures, recurrences, deaths and ERC-adjudicated causes

	Bacteriological failure or recurrence			Clinical failure or recurrence			Deaths (all)	
	Placebo	Rifampicin	p	Placebo	Rifampicin	p	Placebo	Rifampicin
Total randomised	**388**	**370**	**-**	**388**	**370**	**-**	**388**	**370**
Total events	**71 (18.3%)**	**62 (16.8%)**	**0.81**	**86 (22.2%)**	**76 (20.5%)**	**0.84**	**56 (14.4%)**	**56 (15.1%)**
Failure	5 (1.3%)	4 (1.1%)	0.82	25 (6.4%)	23 (6.2%)	0.97		
Failure due to slow resolution	*3 (0.8%)*	*1 (0.3%)*		*17 (4.4%)*	*10 (2.7%)*			
Recurrence	16 (4.1%)	3 (0.8%)	0.01	23 (5.9%)	8 (2.2%)	0.01		
Death without either failure or recurrence	50 (12.9%)	55 (14.9%)	0.30	38 (9.8%)	45 (12.2%)	0.22		
Total failures/recurrences (first two columns) or *S. aureus* related deaths (third column): attributed by Endpoint Review Committee to:	**21 (100%)**	**7 (100%)**		**48 (100%)**	**31 (100%)**		**32 (100%)**	**36 (100%)**
Failure of antibiotics	1 (5%)	0		3 (6%)	1 (3%)		1 (3%)	3 (8%)
Failure of source management	17 (81%)	3 (43%)		38 (79%)	24 (77%)		21 (66%)	18 (50%)
Not recognised	*9 (43%)*	*2 (29%)*		*12 (25%)*	*5 (16%)*		*3 (9%)*	*4 (11%)*
Recognised, not actively managed	*5 (24%)*	*1 (14%)*		*16 (33%)*	*14 (45%)*		*8 (25%)*	*8 (22%)*
Recognised, actively managed still failed/recurred	*3 (14%)*	*0*		*10 (21%)*	*5 (16%)*		*10 (31%)*	*6 (17%)*
Not possible to distinguish	3 (14%)	4 (57%)		7 (15%)	6 (19%)		10 (31%)	15 (42%)
Death a consequence of late presentation	-	-		-	-		3 (9%)	11 (31%)

Subgroup analyses according to the three most important characteristics, time between starting active antibiotics and trial drug, methicillin resistance, and foci of infection (deep versus not deep), suggested no heterogeneity in lack of effect of rifampicin ($p_{heterogeneity}$ 0.42, 0.07, 0.10 respectively, **Figure 5B**. The rifampicin effect varied significantly according to the initial antibiotic given at randomisation, with some suggestion of benefit in those with methicillin-sensitive infection treated with flucloxacillin alone ($p_{heterogeneity}$=0.01, **Figure 6**), but across none of 16 other subgroup analyses ($p_{heterogeneity}$>0.05, **Figure 7**). At the suggestion of a reviewer we also considered subgroup analyses by diabetes ($p_{heterogeneity}$=0.37), weight ($p_{heterogeneity}$=0.13), BMI ($p_{heterogeneity}$=0.58) and dose in mg/kg ($p_{heterogeneity}$=0.42).

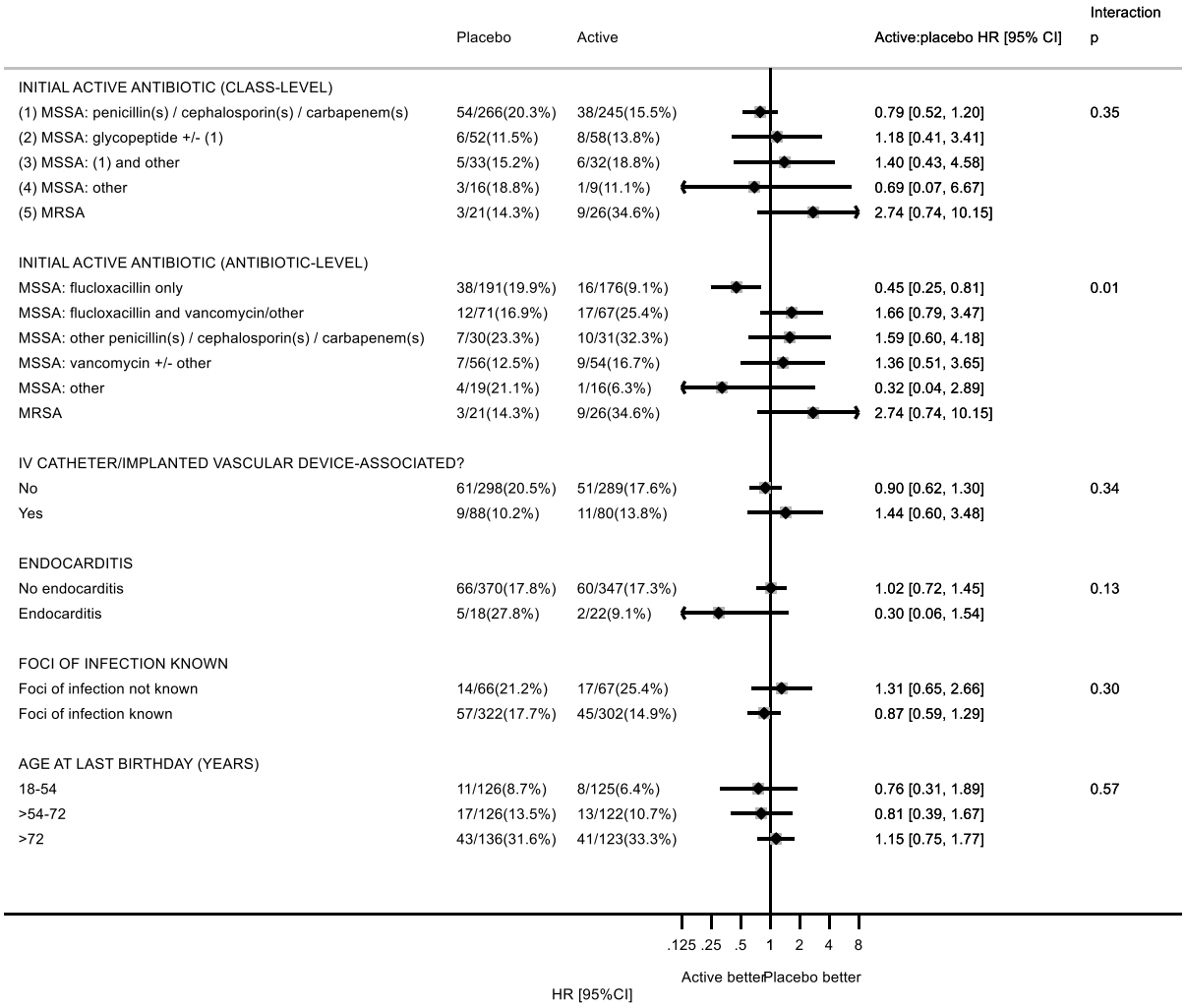
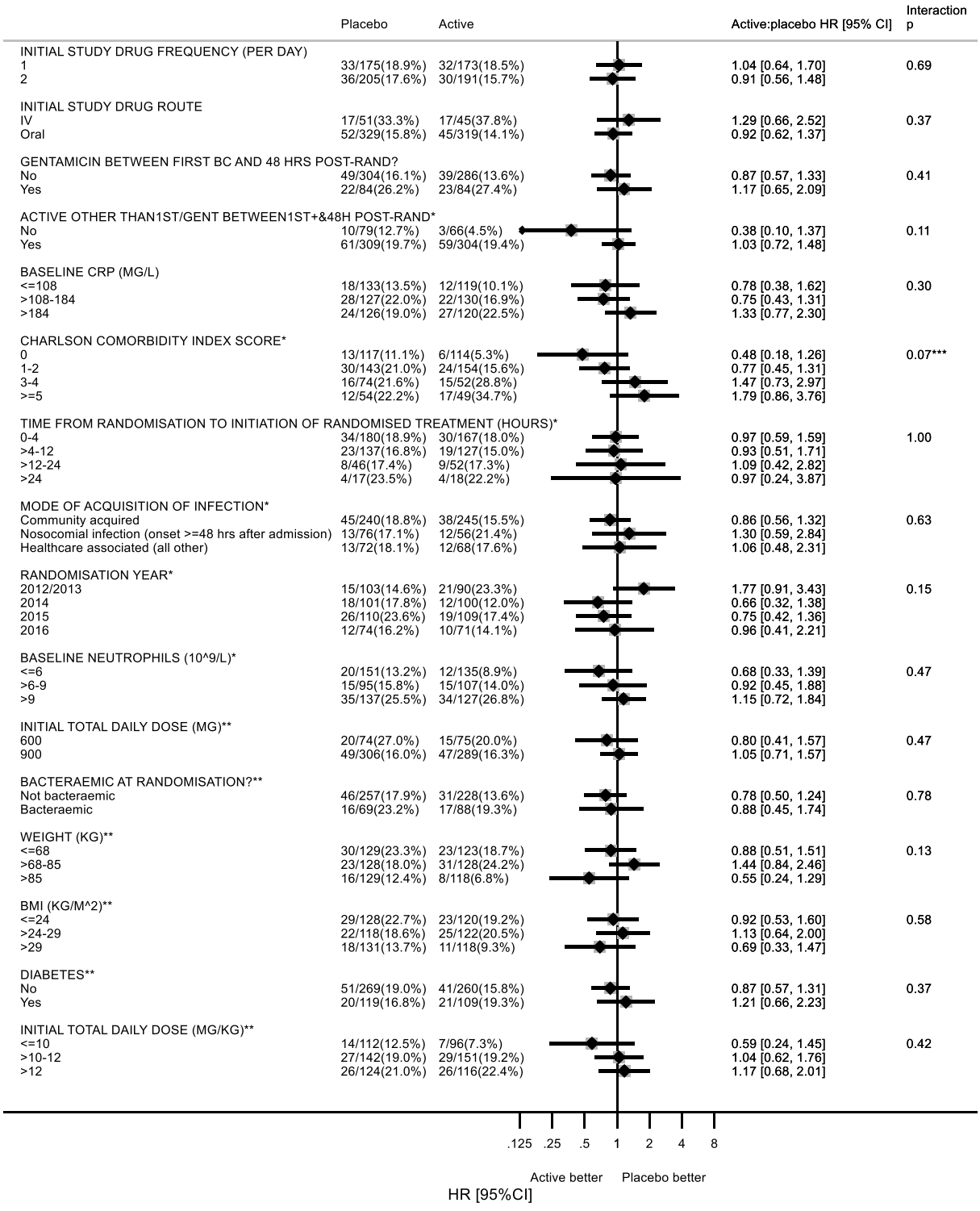


Figure 6 Five other priority subgroup analyses for bacteriological failure/recurrence or death through 12 weeks (primary endpoint)

Note: presenting class-level and antibiotic-level categorisation of initial active antibiotics (as per the Statistical Analysis Plan). See **Figure 5(b)** for the three other priority subgroup analyses defined in the Statistical Analysis Plan (time between starting active antibiotics and trial drug, methicillin resistance and foci of infection (deep versus not deep)). All eight priority subgroup analyses were pre-specified in the protocol and the Statistical Analysis Plan.



* subgroup analysis pre-specified in the statistical analysis plan but not the protocol
** additional subgroup analysis not in protocol or statistical analysis plan
*** p=0.07 using continuous interactions (splines); p=0.01 using continuous interaction (linear)

Figure 7 Twelve other subgroup analyses for bacteriological failure/recurrence or death through 12 weeks (primary endpoint)

Secondary endpoints

Clinically-defined failure/recurrence or death occurred in 76 (20.5%) rifampicin versus 86 (22.2%) placebo participants (RD=-1.4% (95% CI -7.4%,+4.7%); HR=0.97 (0.71-1.32) p=0.84, **Figure 8**). In exploratory post-hoc analyses, comparing rifampicin and placebo there were 23 (6.2%) versus 25 (6.4%) failures (competing-risks p=0.97), 8 (2.2%) versus 23 (5.9%) recurrences (competing-risks p=0.01), and 45 (12.2%) versus 38 (9.8%) deaths without clinically-defined failure/recurrence respectively (competing-risks p=0.22) (**Table 7**). The number-needed-to-treat to prevent one clinically-confirmed recurrence was 26.

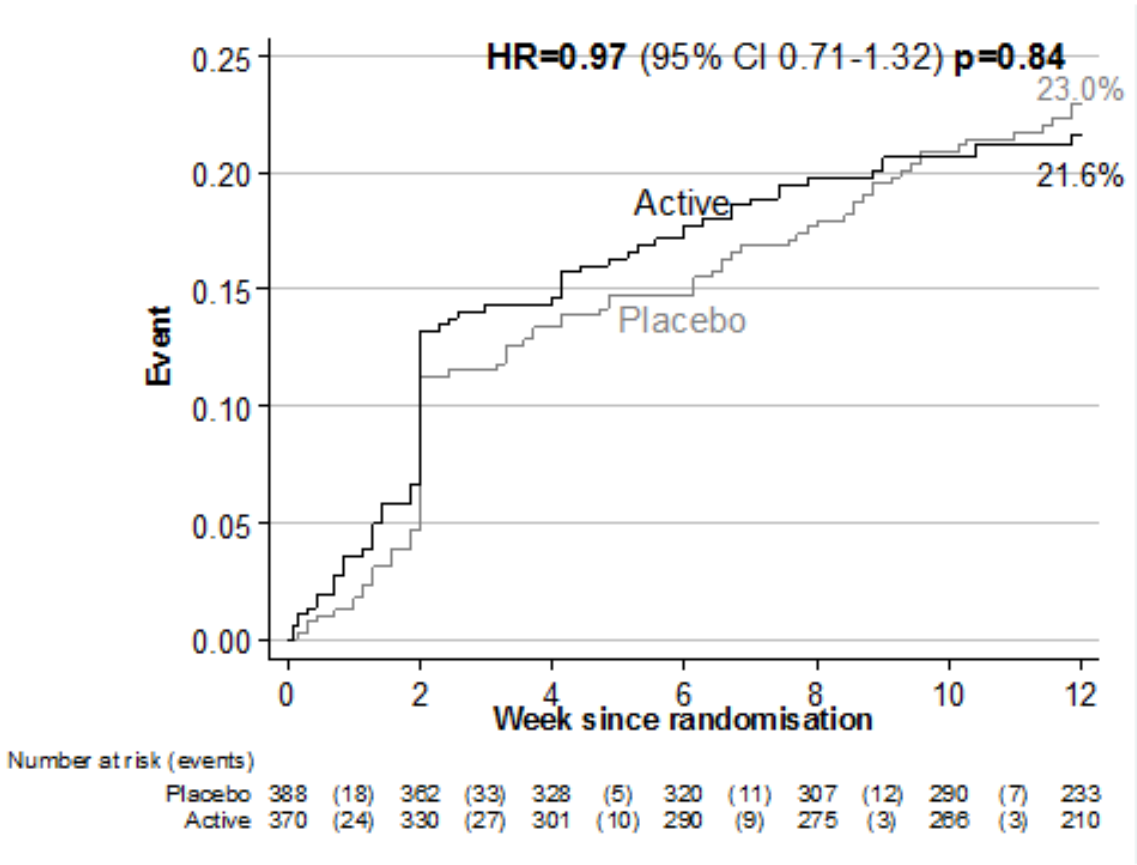


Figure 8 Clinically-defined failure/recurrence or death

The ERC adjudicated that failure of infection focus management was implicated in 38/48 (79%) on placebo versus 24/31 (77%) failures/recurrences on rifampicin (**Table 7**). Of these failures of infection focus management, there were 5 placebo versus 12 rifampicin participants where the focus was not recognized, 16 vs 14 respectively where the focus was recognised but not actively managed (e.g. because it was in an inaccessible site, or other

patient characteristics made intervention impossible) and 10 vs 5 respectively where the focus was recognised, actively managed, but despite this failure/recurrence still occurred. Failure of antibiotic therapy was implicated in the failure/recurrence in only 3 (6%) placebo vs 1 (3%) rifampicin failures/recurrences, with the cause being impossible to distinguish in the remaining 7 (15%) vs 6 (19%) respectively.

By 12-weeks, 56 (15.1%) rifampicin versus 56 (14.4%) placebo participants died (RD=+1.0% (95% CI -4.3%-6.2%); HR=1.10 (0.76-1.60) p=0.60, **Figure 9**). 25 (6.8%) rifampicin versus 17 (4.4%) placebo participants died before 2 weeks (HR=1.60 (0.86-2.95) p=0.13). 14 rifampicin versus 16 placebo deaths were adjudicated definitely *S. aureus*-related, 14 versus 12 probably *S. aureus*-related, and 8 versus 4 possibly *S. aureus*-related, respectively (**Table 27** in **Appendix 2**). 18 versus 23 were not attributed to *S. aureus* (remainder unattributable) (overall p=0.64).

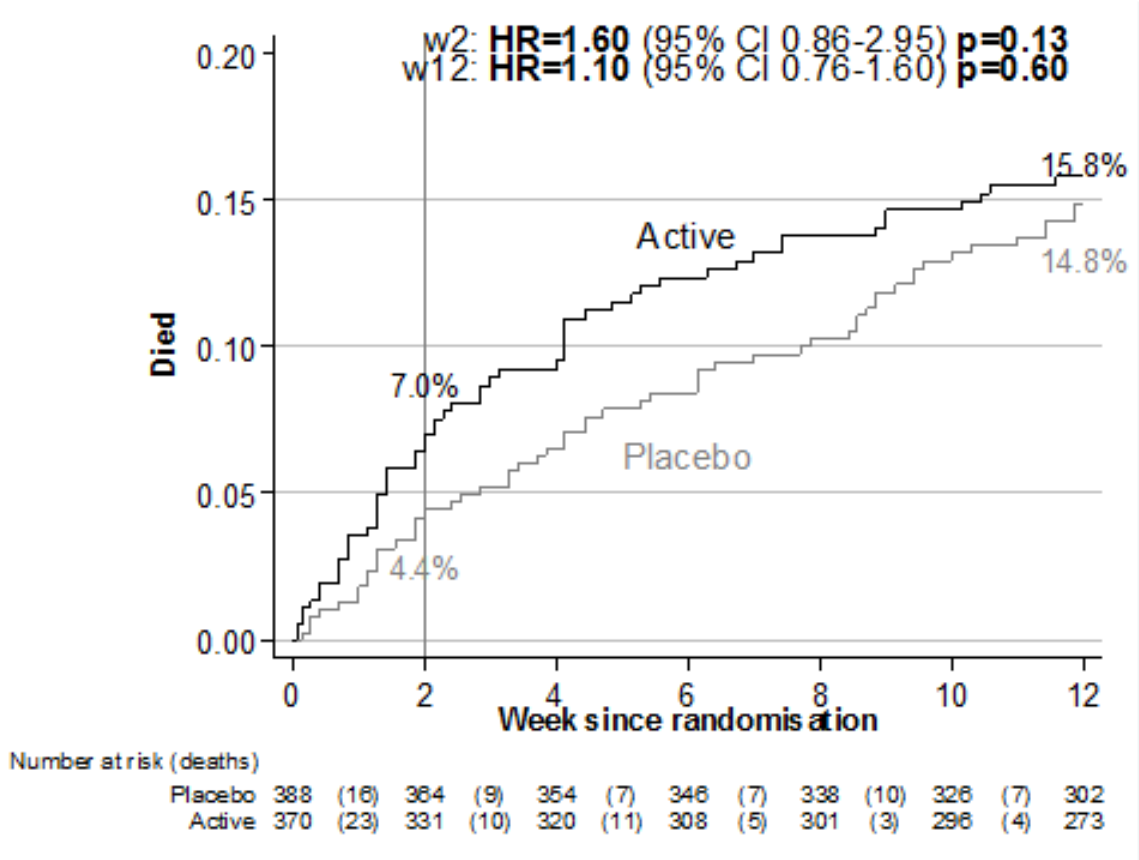


Figure 9 Mortality through 12 weeks

As for clinically-defined and bacteriologically-confirmed failures/recurrences, the ERC adjudicated that failure of infection focus management was implicated in most *S. aureus*-related deaths, 21/32 (66%) on placebo versus 18/36 (50%) on rifampicin (**Table 7**). Of these failures of infection focus management, there were 3 placebo versus 4 rifampicin participants where the focus was not recognized, 8 vs 8 respectively where the focus was recognised but not actively managed and 10 vs 6 respectively where the focus was recognised, actively managed, but despite this the participant still died from *S. aureus*. Failure of antibiotic therapy was implicated in only 1 (3%) placebo vs 3 (8%) rifampicin *S. aureus*-related deaths, with the relationship to antibiotics/focus management being impossible to distinguish in the remaining 10 (31%) vs 15 (42%) respectively. Three (9%) placebo versus 11 (31%) rifampicin *S. aureus*-related deaths were considered to have occurred as a consequence of late presentation to healthcare, i.e. were not preventable.

There was no difference in longer-term (post-week 12) survival between the groups, based on consented updates of vital status from routine electronic health records (p=0.69) (**Figure 10**).

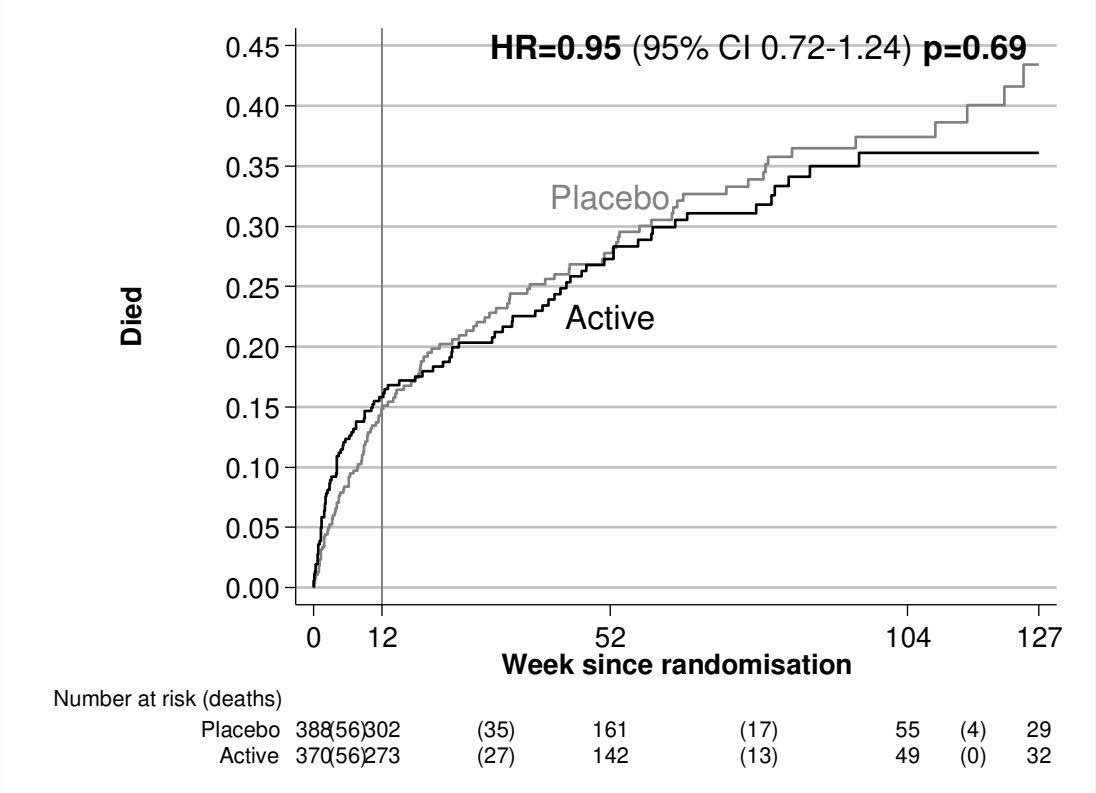


Figure 10 Mortality over the longer-term

Two (0.5%) rifampicin participants developed new rifampicin-resistant *S. aureus* bacteraemia 7 and 42 days after randomisation (p=0.24). One occurred on day 7 (followed by rifampicin discontinuation on day 11 and bacteriological failure on day 14); the other on day 42 (prescribed 14 days rifampicin; bacteriological recurrence on day 42). One additional participant had rifampicin-resistant *S. aureus* isolated from a permanent pacemaker wire removed on day 1 (within 4 hours of the first dose of trial drug). The screening blood culture had isolated a rifampicin-sensitive S. aureus. Further blood cultures were sterile for the remainder of follow-up. Following whole genome sequencing, the rifampicin resistant pacemaker isolate was 11 single nucleotide polymorphisms from the screening isolate and another isolate taken from the pacemaker on day-1, whereas these latter two isolates did not differ genetically, suggesting a diversity between isolates of more than 3 days in origin, and thus suggesting that the patient had a mixed infection with both rifampicin-resistant and rifampicin-susceptible strains that was not detected at screening.

There was no evidence that duration of bacteraemia was significantly shorter in those randomised to rifampicin (Figure 11; global p=0.66). Eighty-eight patients in the rifampicin group had positive blood cultures at enrolment. Of these 88, only one failed bacteriologically, none had bacteriological recurrence and none developed rifampicin-resistant infection. Eight failed clinically (including the one who failed bacteriologically) and two had clinical recurrence.

CRP declined significantly in both rifampicin and placebo groups, but decreases were smaller in rifampicin participants (global p=0.001, **Figure 11** Persistence of bacteraemia).

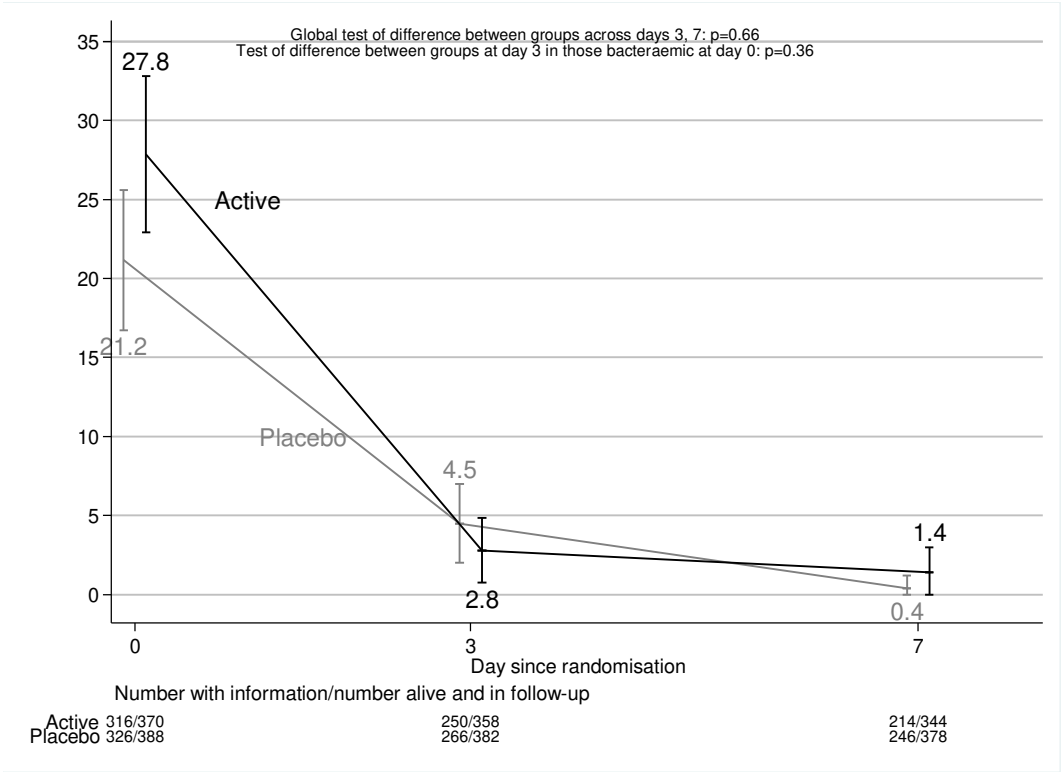


Figure 11 Persistence of bacteraemia

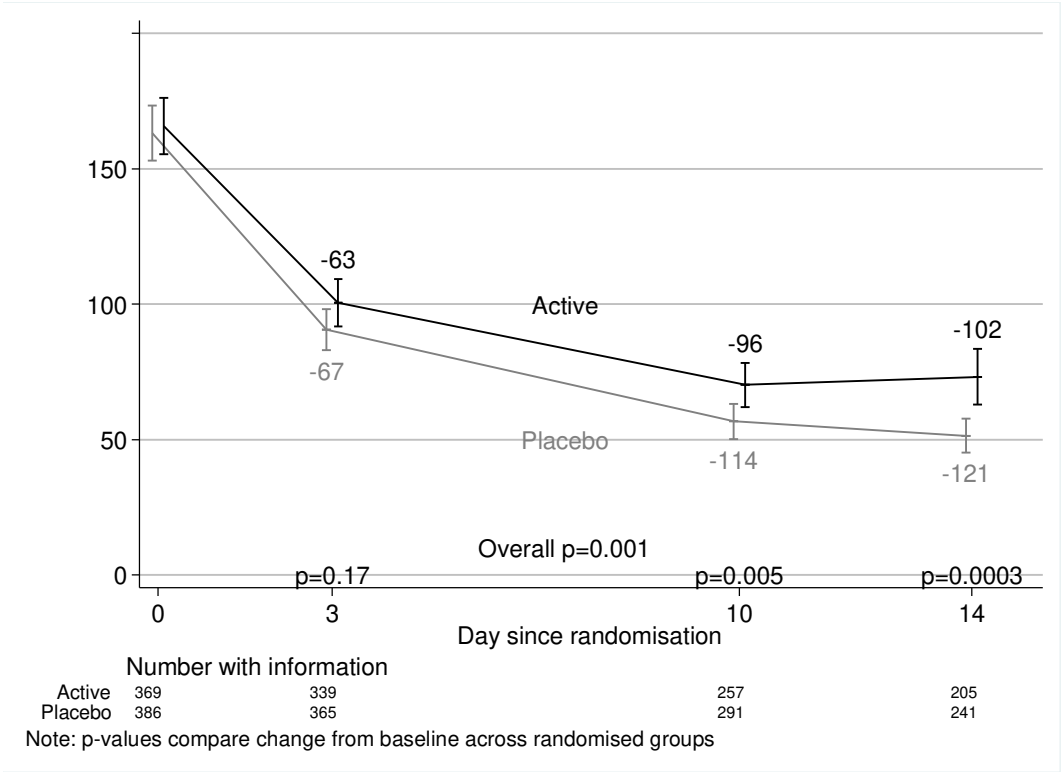


Figure 12 CRP over 2 weeks from randomisation

Safety

By 12-weeks, 101 (27.3%) rifampicin versus 94 (24.2%) placebo participants experienced 112 versus 116 SAEs (HR=1.21 (95% CI 0.92-1.61) p=0.17, **Figure 13**, **Table 8, Table 28** in **Appendix 2**). The most common type of SAE was related to Infections and infestations, the vast majority due to fatal events caused by *S. aureus* bacteraemia (non-fatal *S. aureus*-related adverse events were exempted from adverse event reporting in the protocol to avoid double counting disease failure/recurrence events).

Table 8 Summary of SAEs

SAEs	Placebo N=388	Rifampicin N=370	Total N=758	P
Any SAE	94 (24.2%) 116	101 (27.3%) 112	195 (25.7%) 228	0.36
Infections and infestations	39 (10.1%) 40	37 (10.0%) 38	76 (10.0%) 78	1.00
Cardiac disorders	13 (3.4%) 15	5 (1.4%) 6	18 (2.4%) 21	0.09
Vascular disorders	2 (0.5%) 2	4 (1.1%) 4	6 (0.8%) 6	0.44
Respiratory, thoracic and mediastinal disorders	12 (3.1%) 12	6 (1.6%) 6	18 (2.4%) 18	0.23
Gastrointestinal disorders	7 (1.8%) 7	10 (2.7%) 12	17 (2.2%) 19	0.47
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Renal and urinary disorders	4 (1.0%) 4	10 (2.7%) 10	14 (1.8%) 14	0.11
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	12 (3.1%) 12	11 (3.0%) 11	23 (3.0%) 23	1.00
Investigations	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Injury, poisoning and procedural complications	5 (1.3%) 5	3 (0.8%) 3	8 (1.1%) 8	0.73
Blood and lymphatic system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Metabolism and nutrition disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Psychiatric disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Nervous system disorders	5 (1.3%) 6	2 (0.5%) 2	7 (0.9%) 8	0.45

Note: Showing number of patients with one or more event (% of participants) number of events (e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)

Two rifampicin participants with pre-existing liver disease experienced non-fatal hepatic failure.

One 47-year old female required prolongation of hospitalisation for acute hepatic failure (grade 3) with raised INR (grade 2), ascites (grade 3) and acute renal failure (grade 3) which developed on ICU following 5 days rifampicin (900mg daily) with flucloxacillin. The participant had pre-existing Hepatitis C and chronic liver disease. Acute hepatic and renal failure was considered to have been triggered by sepsis. The participant recovered.

One 51-year-old female required prolongation of hospitalisation for decompensated liver disease (grade 3) with ascites (grade 3) following 14 days rifampicin (initially on 900 mg daily) with flucloxacillin. The participant did not mention liver disease at screening/enrolment and there was nothing in her medical notes regarding any past history of liver problems. When she developed decompensated liver disease with ascites, it was discovered that she had had a previous diagnosis of non-alcoholic steatosis (NASH) at another hospital several years previous, but was no longer under follow up. The participant recovered.

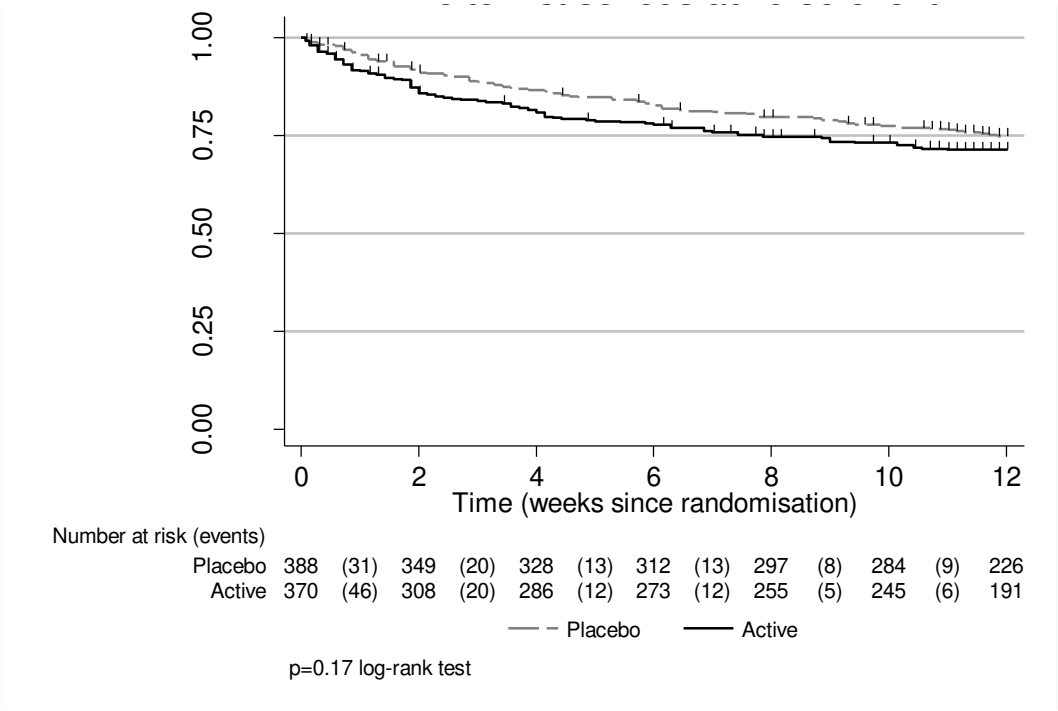


Figure 13 Time to first SAE

129 (34.9%) rifampicin versus 131 (33.8%) placebo participants experienced 209 versus 193 grade 3/4 AEs (HR=1.12 (95% CI 0.88-1.43) p=0.36, **Figure 14, Figure 14** Time to first grade 3 or 4 adverse event

Table 9**, Table 29** in **Appendix 2**). Most notable was a trend towards more renal grade 3/4 AEs with rifampicin which occurred in 19 (5.1%) versus 9 (2.3%) placebo participants (p=0.053); 17 versus 6 respectively being acute kidney injury.

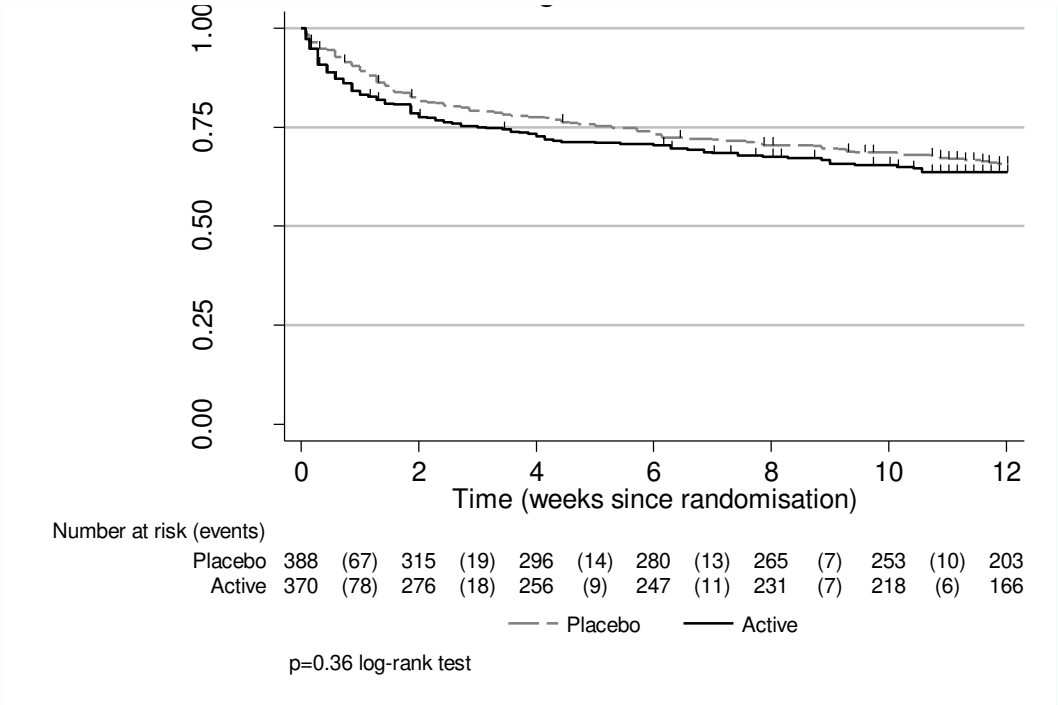


Figure 14 Time to first grade 3 or 4 adverse event

Table 9 Summary of Grade 3/4 adverse events

Grade 3/4 adverse events	Placebo N=388	Rifampicin N=370	Total N=758	P
Any grade 3/4 adverse event	131 (33.8%) 193	129 (34.9%) 209	260 (34.3%) 402	0.76
Infections and infestations	45 (11.6%) 53	40 (10.8%) 48	85 (11.2%) 101	0.82
Cardiac disorders	15 (3.9%) 17	6 (1.6%) 8	21 (2.8%) 25	0.08
Vascular disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Respiratory, thoracic and mediastinal disorders	16 (4.1%) 17	10 (2.7%) 11	26 (3.4%) 28	0.32
Gastrointestinal disorders	21 (5.4%) 24	29 (7.8%) 40	50 (6.6%) 64	0.19
Hepatobiliary disorders	0 (0.0%) 0	3 (0.8%) 3	3 (0.4%) 3	0.12
Skin and subcutaneous tissue disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Musculoskeletal and connective tissue disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Renal and urinary disorders	9 (2.3%) 9	19 (5.1%) 20	28 (3.7%) 29	0.053
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Reproductive system and breast disorders	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	11 (2.8%) 11	12 (3.2%) 12	23 (3.0%) 23	0.83
Investigations	6 (1.5%) 6	11 (3.0%) 16	17 (2.2%) 22	0.22
Injury, poisoning and procedural complications	6 (1.5%) 6	5 (1.4%) 5	11 (1.5%) 11	1.00
Surgical and medical procedures	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Blood and lymphatic system disorders	3 (0.8%) 3	5 (1.4%) 6	8 (1.1%) 9	0.50
Metabolism and nutrition disorders	3 (0.8%) 3	5 (1.4%) 6	8 (1.1%) 9	0.50
Psychiatric disorders	5 (1.3%) 5	5 (1.4%) 6	10 (1.3%) 11	1.00
Nervous system disorders	11 (2.8%) 14	4 (1.1%) 4	15 (2.0%) 18	0.12
Eye disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00

Note: Showing number of patients with one or more event (% of participants) number of events (e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)

63 (17.0%) rifampicin versus 39 (10.1%) placebo experienced 89 versus 52 antibiotic-modifying AEs (sub-distribution HR=1.78 (1.20-2.65) p=0.004; **Figure 15**, **Figure 15** Time to first antibiotic-modifying adverse event

Table 10, **Table 30** in **Appendix 2**). Gastrointestinal disorders (24 versus 8 participants, respectively, p=0.003) and renal/urinary disorders (8 versus 1 participants, respectively, p=0.02) were more common with rifampicin, as were events classified as general disorders and administration site conditions (13 vs 4 participants), which included some drug interactions (see below).

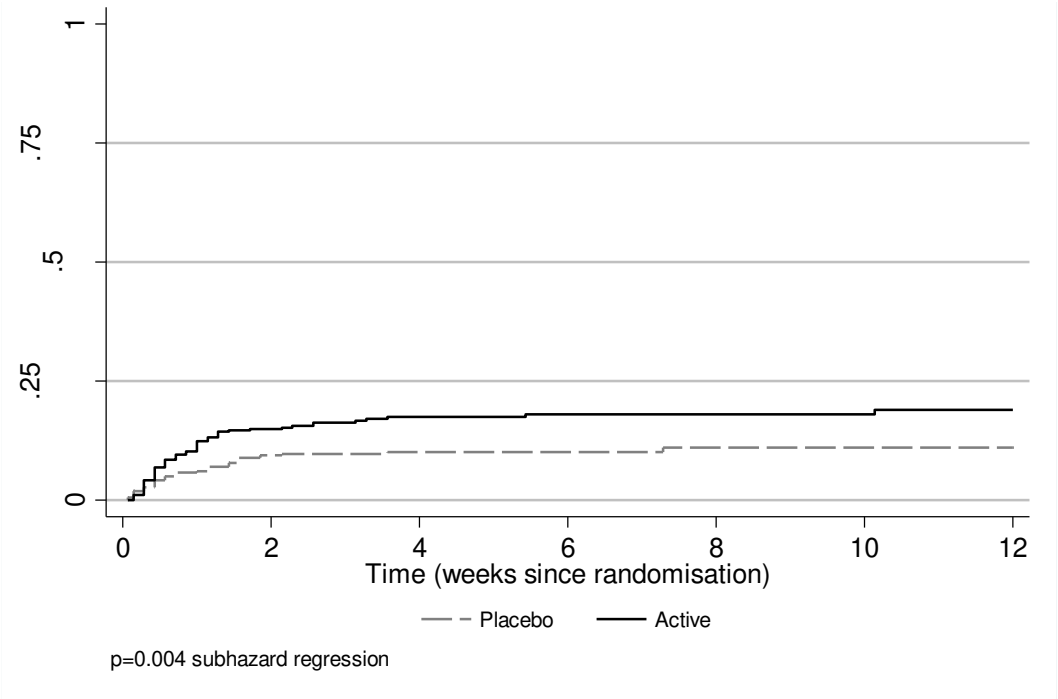


Figure 15 Time to first antibiotic-modifying adverse event

Table 10 Summary of antibiotic-modifying adverse events

Antibiotic-modifying adverse events	Placebo N=388	Rifampicin N=370	Total N=758	P
Any antibiotic-modifying adverse event	39 (10.1%) 52	63 (17.0%) 89	102 (13.5%) 141	0.006
Infections and infestations	3 (0.8%) 3	5 (1.4%) 5	8 (1.1%) 8	0.50
Respiratory, thoracic and mediastinal disorders	2 (0.5%) 4	0 (0.0%) 0	2 (0.3%) 4	0.50
Gastrointestinal disorders	8 (2.1%) 9	24 (6.5%) 32	32 (4.2%) 41	0.003
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	7 (1.8%) 9	8 (2.2%) 9	15 (2.0%) 18	0.80
Renal and urinary disorders	1 (0.3%) 2	8 (2.2%) 10	9 (1.2%) 12	0.02
General disorders and administration site conditions	4 (1.0%) 4	13 (3.5%) 13	17 (2.2%) 17	0.03
Investigations	12 (3.1%) 13	12 (3.2%) 14	24 (3.2%) 27	1.00
Injury, poisoning and procedural complications	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
Blood and lymphatic system disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Metabolism and nutrition disorders	2 (0.5%) 3	0 (0.0%) 0	2 (0.3%) 3	0.50

Antibiotic-modifying adverse events	Placebo N=388	Rifampicin N=370	Total N=758	P
Psychiatric disorders	1 (0.3%) 2	0 (0.0%) 0	1 (0.1%) 2	1.00
Nervous system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00

Note: Showing number of patients with one or more event (% of participants) number of events
(e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)

24 (6.5%) rifampicin versus 6 (1.5%) placebo experienced drug-interactions with antibiotics or other drugs (p=0.0005); 13 versus 4 led to discontinuation of trial drug (p=0.03), 14 versus 3 respectively led to grade 1/2 AEs (p=0.006), and 5 versus 2 respectively to grade 3/4 AEs (p=0.27).

There was no evidence of differences between groups in changes in ALT (global p=0.18, **Figure 16**) or alkaline phosphatase (global p=0.11, **Figure** 16 ALT over 2 weeks from randomisation

). Bilirubin increased significantly in the rifampicin group at day-3 (p<0.0001; global p<0.0001; **Figure 17** Alkaline phosphatase over 2 weeks from randomisation

). Very few participants experienced grade 3 or 4 elevations in these laboratory parameters (**Table 11**).

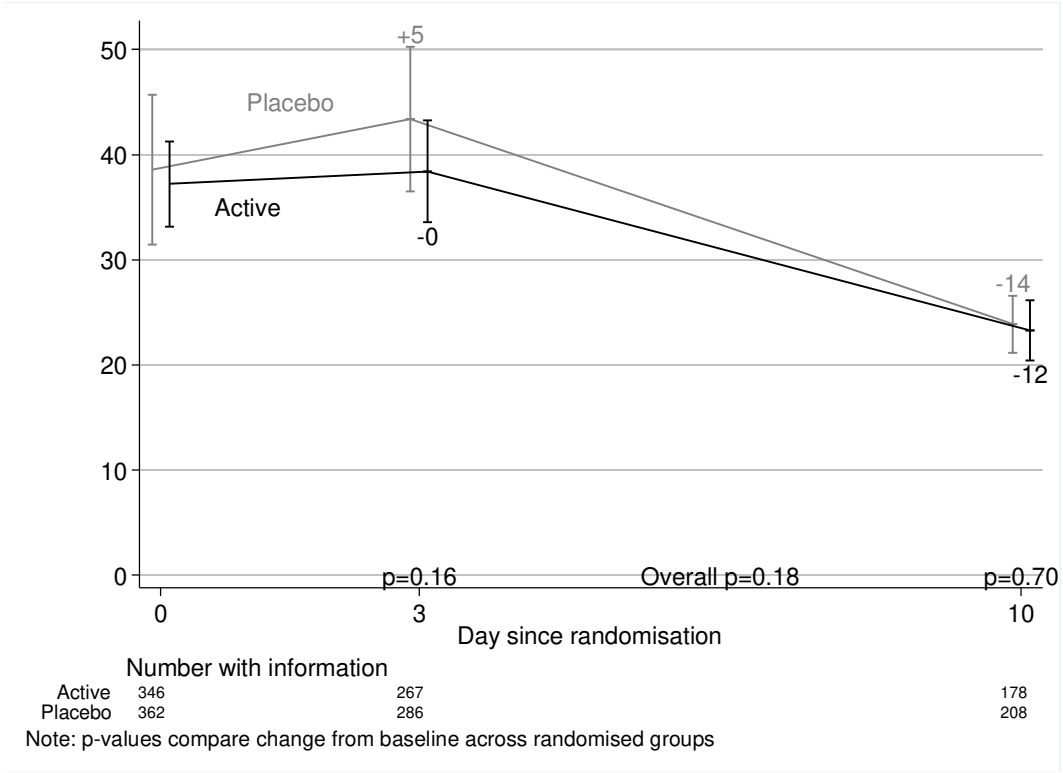


Figure 16 ALT over 2 weeks from randomisation

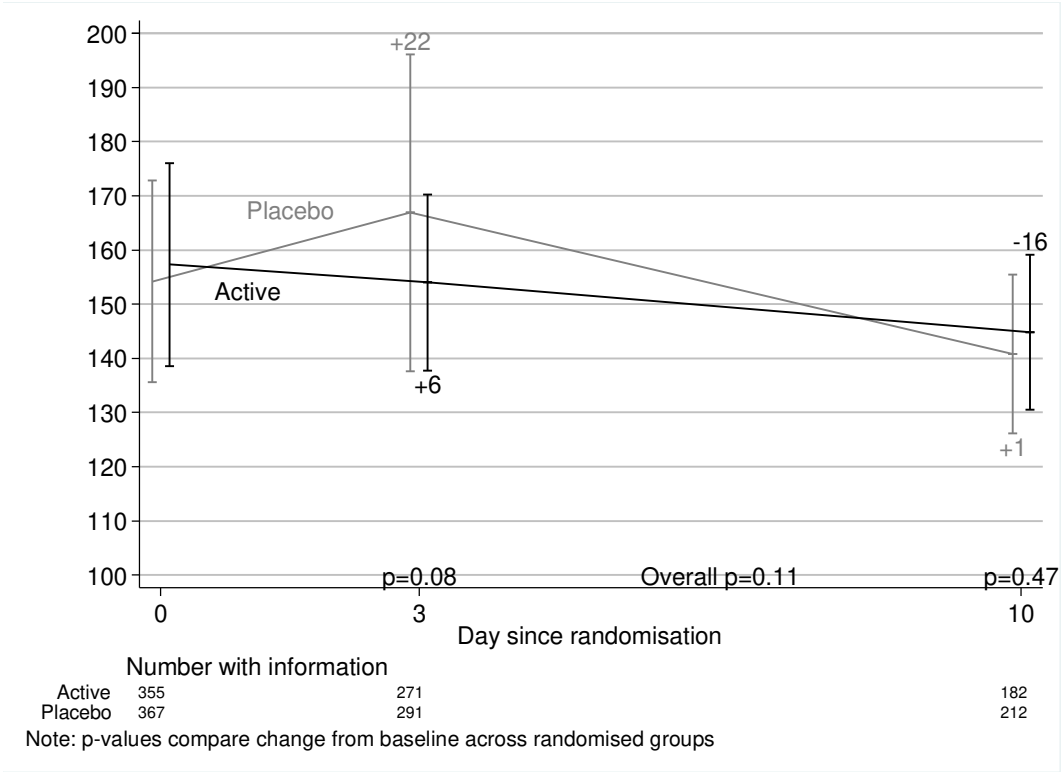


Figure 17 Alkaline phosphatase over 2 weeks from randomisation

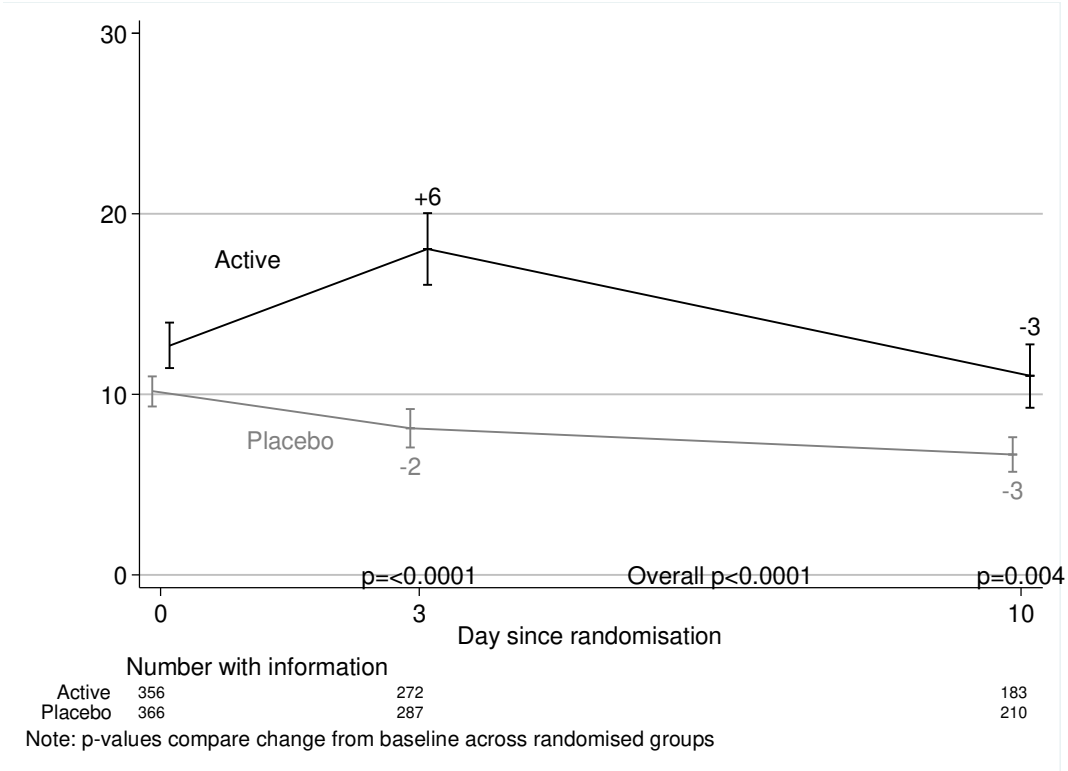


Figure 18 Bilirubin over 2 weeks from randomisation

Table 11 Graded toxicity in ALT, alkaline phosphatase and bilirubin

	Placebo	Active	Total
ALT - Day 0			
Normal	274 (74.5%)	268 (75.1%)	542 (74.8%)
>ULN - 3.0 x ULN (grade 1)	85 (23.1%)	81 (22.7%)	166 (22.9%)
>3.0 - 5.0 x ULN (grade 2)	6 (1.6%)	5 (1.4%)	11 (1.5%)
>5.0 - 20.0 x ULN (grade 3)	2 (0.5%)	3 (0.8%)	5 (0.7%)
>20.0 x ULN (grade 4)	1 (0.3%)	0 (0.0%)	1 (0.1%)
ALT - Day 3			
Normal	202 (70.6%)	203 (76.0%)	405 (73.2%)
>ULN - 3.0 x ULN (grade 1)	70 (24.5%)	50 (18.7%)	120 (21.7%)
>3.0 - 5.0 x ULN (grade 2)	8 (2.8%)	12 (4.5%)	20 (3.6%)
>5.0 - 20.0 x ULN (grade 3)	6 (2.1%)	2 (0.7%)	8 (1.4%)
ALT - Day 10			
Normal	182 (87.5%)	160 (89.9%)	342 (88.6%)
>ULN - 3.0 x ULN (grade 1)	24 (11.5%)	17 (9.6%)	41 (10.6%)
>3.0 - 5.0 x ULN (grade 2)	2 (1.0%)	1 (0.6%)	3 (0.8%)
Alkaline phosphatase - Day 0			
Normal	267 (71.8%)	252 (69.2%)	519 (70.5%)
>ULN - 2.5 x ULN (grade 1)	90 (24.2%)	101 (27.7%)	191 (26.0%)
>2.5 - 5.0 x ULN (grade 2)	13 (3.5%)	9 (2.5%)	22 (3.0%)
>5.0 - 20.0 x ULN (grade 3)	2 (0.5%)	2 (0.5%)	4 (0.5%)
Alkaline phosphatase - Day 3			
Normal	196 (67.4%)	175 (64.6%)	371 (66.0%)
>ULN - 2.5 x ULN (grade 1)	82 (28.2%)	91 (33.6%)	173 (30.8%)
>2.5 - 5.0 x ULN (grade 2)	11 (3.8%)	2 (0.7%)	13 (2.3%)
>5.0 - 20.0 x ULN (grade 3)	1 (0.3%)	3 (1.1%)	4 (0.7%)
>20.0 x ULN (grade 4)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Alkaline phosphatase - Day 10			
Normal	149 (70.3%)	119 (65.4%)	268 (68.0%)
>ULN - 2.5 x ULN (grade 1)	57 (26.9%)	58 (31.9%)	115 (29.2%)
>2.5 - 5.0 x ULN (grade 2)	6 (2.8%)	5 (2.7%)	11 (2.8%)
Bilirubin - Day 0			
Normal	341 (91.7%)	309 (85.1%)	650 (88.4%)
>ULN - 1.5 x ULN (grade 1)	14 (3.8%)	31 (8.5%)	45 (6.1%)
>1.5 - 3.0 x ULN (grade 2)	17 (4.6%)	17 (4.7%)	34 (4.6%)
>3.0 - 10.0 x ULN (grade 3)	0 (0.0%)	6 (1.7%)	6 (0.8%)
Bilirubin - Day 3			
Normal	270 (94.1%)	190 (69.9%)	460 (82.3%)
>ULN - 1.5 x ULN (grade 1)	11 (3.8%)	35 (12.9%)	46 (8.2%)
>1.5 - 3.0 x ULN (grade 2)	3 (1.0%)	35 (12.9%)	38 (6.8%)
>3.0 - 10.0 x ULN (grade 3)	3 (1.0%)	12 (4.4%)	15 (2.7%)
Bilirubin - Day 10			
Normal	200 (95.2%)	162 (88.5%)	362 (92.1%)
>ULN - 1.5 x ULN (grade 1)	6 (2.9%)	7 (3.8%)	13 (3.3%)
>1.5 - 3.0 x ULN (grade 2)	4 (1.9%)	12 (6.6%)	16 (4.1%)
>3.0 - 10.0 x ULN (grade 3)	0 (0.0%)	2 (1.1%)	2 (0.5%)

Chapter 4 Trial Participation Qualitative Sub-study

(Note: this chapter includes material that has been adapted from the trial protocol which has been published in Trials 2012 13:241.)

Experiences of being approached for trial participation, the consenting process and trial participation

The overall objective of this sub-study was to identify patient and personal legal representative barriers to recruitment. The study was led by Jennifer Bostock, the trial PPI representative. The sub study had two components: the first involved patients/legal representatives who **did not** consent to trial recruitment, and the second involved patients/legal representatives who **did** consent to trial recruitment.

Patient/legal representatives who did not consent to trial recruitment

The overall objective of this sub-study was to identify patient and legal representative barriers to recruitment, in order:

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.

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 were given a short, completely anonymous, questionnaire with a freepost envelope, which could be completed at any time in the future and posted directly to the MRC Clinical Trials Unit at UCL. 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 were also be provided with a parallel questionnaire.

At the Guy's and St Thomas' centre, at the end of the questionnaire, participants/legal representatives were offered the option of being interviewed by the ARREST PPI advisor. If they agreed to be interviewed, they were asked to provide their name and contact details, and this would indicate consent for an interview. The aim was to get experiences from ~3 participants and ~3 personal 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 followed the questions in the questionnaire, seeking to obtain a more complete narrative of experiences around each aspect.

Patient/legal representatives who did consent to trial recruitment

The overall objective was to sample views on experiences of trial participation: to assess what participants or their (personal) legal representatives liked, and what they did not like and think could have been done better. This was in order:

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 (at the time) 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 were 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 was an interview study conducted at one centre, Guy's and St Thomas' NHS Trust. Since participants were typically very unwell when they joined the study, the approach to each patient to discuss the interview study and seek additional consent was made at a varying time after randomisation depending on clinical status. For most patients this was between 2-3

weeks from randomisation, when their clinical status had improved and discharge was being planned. However, it could have been at any time up to their final 12 week ARREST follow-up visit. The research nurse provided an additional information sheet 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 agreed and provided consent for this additional interview, then the ARREST PPI advisor conducted the interview on the telephone at a time that was convenient for the participant. Participants who gave consent originally or subsequently and legal representatives who gave consent for relative/friend participation were approached.

The aim was to get experiences from ~3 participants and ~3 personal legal representatives (who were 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 was semi-structured. The first set of questions explored 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?

The second set of questions explored 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 (i.e. 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).

Findings

The study revealed two findings: firstly there was a disappointing uptake of both questionnaire completion and interview. 20 questionnaires were sent and only 7 responded and 3 patients/legal representatives were interviewed. Whilst it was expected that the study would be challenging and unorthodox in such a trial (especially seeking to explore views of those who did not consent), it was not anticipated that uptake would be as low as it was.

For patients who **did not** consent, the reasons given were:

'*Everything else going on was too much*', *'could not make a decision either way', 'best to play safe', 'felt too ill/tired', 'did not have enough time to decide'*. Another added, *"would have liked to take part but the side effects were too risky & I didn't want to take any risks. Everything was explained really well, sorry I couldn't help*". The same patient said that, *'more time to decide'* was very important and would have improved the likelihood of him participating. Another patient who gave similar reasons said that s/he would have been more likely to have participated if the, *'information sheet was shorter'*.

One questionnaire was sent back without any questions being answered but with a narrative arguing that it was not appropriate for patients who were, *"very unwell in A&E. to be hassled by a research nurse about studies that are going on"*. The patient went on to state, *"I fully understand and appreciate trials take place and have taken part in clinical trials. Timing is the key & explaining when people feel a bit more human and can think straight about partaking when they have had time to read & digest it*." Whilst this was only one patient it is

important that all studies seeking to recruit those with serious illness do so in a manner which is sensitive to the needs of patients. The fact that only one patient used the questionnaire or interview as an opportunity to complain in this way is evidence of the careful and considerate method of recruitment displayed by the recruiting staff.

Reasons given by personal legal representatives why they did NOT want their relative to participate were:

'Felt too worried', too much responsibility', 'worried that my relative might ***GET*** *the study drug' = 'worried about side effects and liver problems'.*

For patients who **did** consent, the reasons given were:

"I didn't really need time to think about it, I was ill and so it's all rather difficult" & *"I don't remember what the information sheet was like but Karen explained it all to me and I don't think I had any questions, but I'm sure she would have answered them if I had some".* Another said, *"It's not about the information, I just thought well I've got nothing to lose, but I did ask them to come back the next day and I thought about it, asked some people and still came to the same conclusion that I had nothing to lose so the next day I just signed up".*

The reasons given by personal legal representatives why they consented to their relative participating were:

"To help my mum and perhaps other people, it's a 50/50 chance of her getting the medicine or the placebo and I just thought she might be helped". On the information given they said, *"But to be honest I don't think I even read that sheet. Well I suppose the stuff about safety they told me about and I read it, it wasn't difficult to understand. I just signed it and they were helpful the people who told me about it".*

What have we learned?

Despite the limited responses it is possible to draw some lessons for the future from this small study. These are:

1. Some things researchers cannot change but others they can. The *'felt too ill/tired & 'had too much going on"* might be decreased if researchers delayed recruitment until the patients feel a little better (although this was not be possible in the present trial given the requirement for <96 hours of treatment).
2. Similarly *'not enough time to decide'* is something that can be changed, *'Information sheet too long'* can also be altered.
3. More subtle and challenging adaptations might come when consideration is given to comments such as, *'worried that my relative might GET the study drug'*. Whilst honesty is paramount, promoting the reason for the trial and the reason why this medicine is being studied might help sway the balance in favour of the risk being worth taking.

CONCLUSION

It is unusual for a trial such as this to explore these issues and it is challenging ethically to gain approval to conduct a study approaching patients/representatives who did not consent to participate in the primary study. However it was deemed important both by the trial team for this and future research, and by our PPI advisor for the benefit of patients and their representatives. Having gained ethical approval for this study and having learned lessons on how to improve in future we are confident that other research will benefit from the lessons, methods and findings of this small study. A number of practical suggestions were made based upon the findings and were presented at an Investigator meeting by the PPI advisor. It is hoped that these suggestions and the model for this sub study will be used by those at the meeting and their wider research networks.

Chapter 5 Economic and Health-Related Quality of life consequences of *S. aureus* bacteraemia, and effect of treatment with adjunctive rifampicin

Introduction

The ARREST trial was designed to evaluate the efficacy of adjunctive rifampicin in reducing bacteriologically-confirmed failure or recurrence of *S. aureus* bacteraemia or death in 12 weeks. The trial did not provide evidence that rifampicin improves the composite primary endpoint. However, analyses of the components of this composite primary endpoint suggested that adjunctive rifampicin reduced the risk of disease recurrence. Nevertheless, the trial did not find any impact of rifampicin on short- or longer-term mortality (secondary outcomes). Rifampicin also significantly complicated other drug treatment. Hence, clinically, adjunctive rifampicin was not considered to provide overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

The trial's pragmatic design means the population included is clinically relevant, and non-comparative findings can be considered generalisable. The clinical results highlight the severity of *S. aureus* bacteraemia and also show the high degree of heterogeneity in the patient population. In this component of the analyses, we firstly describe the trial evidence on the Health Related Quality of Life (throughout abbreviated to HRQoL) and economic consequences of an *S. aureus* bacteraemia episode in this patient population – which can inform the burden to patients (in terms of HRQoL) and to health systems (in terms of health system costs). We also explore heterogeneity by evaluating determinants of costs and HRQoL. Quantifying the burden of *S. aureus* bacteraemia allows better informed future evaluations of alternative treatment and prevention strategies, a research area which has been highlighted.[35] Whilst the literature on the economic impact of *S. aureus* bacteraemia is substantial, particularly for methicillin-resistant strains (MRSA), the evidence it is based on is poor and often does not rely on any empirical data.[36]

Whilst evaluation of the costs and HRQoL impacts of *S. aureus* bacteraemia, and potential determinants of these, are the main focus of our analyses, given the trial's primary aim we will also investigate the effect of adjunctive rifampicin on HRQoL and cost outcomes. From the results of the clinical analyses it can be hypothesised that rifampicin adjunctive treatment may be associated with cost savings and improvements in HRQoL via the small but significant reduction in bacteriologically and clinically-defined disease recurrences

(hypothesised to arise from the sterilisation of deep infection foci). The trial data will be used to determine the potential cost-effectiveness of adjunctive rifampicin treatment, and given the likely high degree of uncertainty, the value of further research will be determined.

Methods

Cost and health outcomes for patients with *S. aureus* bacteraemia were evaluated using data from the ARREST trial. Health outcomes were measured as quality-adjusted life years (QALYs). The QALY combines survival and health-related quality of life (HRQoL) into a single metric, where time spent with poorer HRQoL is downweighted. Costs considered in analysis were those incurred by the NHS and Personal Social Services (PSS), as recommended by the National Institute for Health and Care Excellence (NICE).[37] Costs and QALYs were measured only for 84 days (i.e. 12 weeks) from the date of randomisation, which was also the maximum duration of active follow-up (longer follow-up through electronic health records was done only for mortality). When considering determinants of costs and QALYs, the effect of adjunctive rifampicin was evaluated, which allowed for a cost-effectiveness analysis to be conducted. Given the short time horizon, neither costs nor health benefits were discounted. The analysis was conducted using the statistical software R version 3.4.1.[38]

Details of each component of analyses (analyses of health benefits; analysis of costs; and analysis of cost-effectiveness and value of information) are presented below. This is followed by a description of the statistical methods used.

Costs

Data on the use of *S. aureus* bacteraemia-related healthcare resources was collected during the trial and served as the basis for the calculation of total costs included in this analysis. Data related to three different resource use categories:

a) All antibiotic therapy received from randomisation in the active follow-up period (84 days), including trial drug and any other antibiotic therapy used;
b) First admissions and re-admissions to secondary care and length of stay, including investigations and procedures undertaken while hospitalised;
c) Consultations with healthcare providers (in primary or secondary care) after hospital discharge from first hospital admission.

See **Appendix 3** for the resource use questions on the electronic case record forms. Costs for each trial participant were calculated as the product of health resources used during the trial follow-up period and the relevant NHS unit costs. Unit costs were based on the NHS Reference Cost (NHS-RF) data for 2013/14[39] and 2015/16,[40] the Unit Costs of Health and Social Care 2016 (PSSRU),[41] the British National Formulary (BNF),[42] and relevant literature. All values are in British pound sterling (£) and were, where required, updated to 2016 prices.[hospital and community health services (HCHS) index provided by the PSSRU 2016]

Antibiotic therapy

Antibiotic regimens used during the trial were costed using information on the agent, dose, frequency and route of administration. For rifampicin this information was recorded in trial drug logs by healthcare professionals until the earlier of 14 days or cessation of 'backbone' antibiotics. Time (in days) from initiation to end of randomised treatment was estimated and used to estimate the overall on trial drug cost per patient during follow-up period. The use of other antibiotics was recorded by healthcare professionals in treatment logs completed at each change in therapy until end of follow-up or death. Time (in days) on other antibiotics was also estimated and was mainly informed by administration 'start' and 'stop' information. Only antibiotics taken after randomisation were considered. As for the trial drug, estimated time (in days) on other antibiotics only considered time from randomisation.

Table 31A in **Appendix 2** lists, for all antibiotic therapies costed in the trial, including the trial drug, the unit costs by dose and route of administration. **Table 31B** lists antibiotic therapies by dose and route for which a unit cost was not obtained.

Admissions to secondary care

With regards to hospital inpatient stay, health resource utilisation was recorded by study personnel at weekly clinical assessments until discharge, and then at the final day 84 follow-up visit. These include days spent in wards, including Intensive Care (ITU), or High Dependency Units (HDU), or investigations and procedures (e.g. computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, PET (positron emission tomography scan). Haematology and biochemistry test results were only collected at specific time points, thus were not included. The use of other drugs and the consequences of drug-drug interactions or adverse events were not collected. Hospital readmission information provided at the final day-84 visit was also considered; this included readmission as hospital day cases, readmissions with hospital stay to hospital ward, ITU or HDU, together with all procedures undertaken

after re-hospitalisation. As trial patients were expected to have a long stay in hospital in their initial hospitalisation (i.e. number of days from admission to hospital to first post-enrolment discharge), unit costs from non-elective long stay tariffs were used. This analysis used only days in hospital after randomisation (in contrast with chapter 3 that looked at duration of the entire admission). The unit costs used to calculate the cost of secondary-care-related health consumption in the trial are summarised in **Table 32** in **Appendix 2**.

Consultations with healthcare providers

Data on the number of consultations with healthcare providers were available for discharged patients from participant-reported questionnaires at the final 84-day follow-up. For the period since discharge, each trial participant recorded the number of GP consultations (either at doctor's surgery or at home) and number of hospital outpatient visits with a doctor or nurse, separating the number of those that were *S. aureus* bacteraemia-related from those that were not. All health consultations reported were included in the economic analysis. The unit costs used to cost these are again summarised in **Table 32** in **Appendix 2**.

Health-related quality of life

The health outcome used was total QALYs over 84 days (i.e. period of active follow-up). Data on the EQ-5D-3L instrument, a widely recognised and validated HRQoL descriptive system,[43,44] was collected at baseline and at 7, 14 and 84 days. The recent five-response version of the EQ-5D, the EQ-5D-5L, and associated UK-specific valuation set were not fully available at the start of this study.

The EQ-5D-3L questionnaire has five questions, each relating to a different health dimension: mobility, self-care, ability to undertake usual activity, pain and anxiety/depression. Each question allows three possible responses: no problems, moderate problems and severe problems. Based on their answers, participants can hence be classified as 1 of 243 possible health states *plus* death and unconscious health states. A separate algorithm was then applied to identify the impact of the particular health state on HRQoL, i.e. a weight, where full health assumes a value of 1, death a value of zero, and where values below zero represent health states worse than death. The algorithm used to generate the weights was based on a population study that elicited societal preferences using a time trade-off technique (a technique that, for instance, asks participants how many years in the current health state they would be willing to 'trade off' for a shorter period in full health).[45,46]

In this study, QALYs were estimated using the area under the curve method with interpolation of EQ-5D-3L index scores measured at the beginning and end of each time interval. Hence, for each study participant, and when sufficient data available, a QALY estimate was obtained considering the product of the mean EQ-5D-3L index score during the interval and the duration of the interval.[49]

Statistical methods of analyses

Missingness

Given that the population recruited into the trial contain a proportion of critically ill patients, we expected non-negligible missingness on the EQ-5D data. It is typical of trials in very sick participants, such as ARREST, to recruit or have during the follow-up period, a non-negligible proportion of individuals in a coma. To these patients (n=80 (10.6%) at baseline; n=48 at 7 days; n=38 at 14 days; and n=4 at 84 days) a HRQoL weight of -0.402 was assigned.(48, 49) Some patients were also reported to be unable/unwilling to provide EQ-5D answers (n=20 (2.6%) at baseline; n=18 at 7 days; n=12 at 14 days; and n=10 at 84 days). These patients were assumed to have a HRQoL weight value of -0.261, corresponding to the bottom decile of the EQ-5D index score distribution of all trial patients for which a EQ-5D index score was available. As a sensitivity analysis EQ-5D answers for unable/unwilling patients were kept missing.

In the estimation of QALYs over the 84-day period, interpolation between adjacent assessments was used. Where EQ-5D information was missing at 7 and/or 14 days interpolation used the other (non-missing) assessments. Non-optimal imputation techniques, such as Last Observation Carried Forward/Backward (LOCF/B), were not implemented due to the clear observed differences between mean EQ-5D data at 7 days and baseline and between mean EQ-5D data at 14 days and 84 days.

Missing values of the outcome variable QALYs over the active follow-up period (i.e. 84 days) that could not be interpolated as above were dealt with formally using multiple imputation,[50] a statistical technique that imputes with uncertainty based on the observed characteristics of patients or of the disease, i.e. an assumption of missing-at-random. This technique imputes with uncertainty by creating, at a first stage, several plausible imputed datasets and, in a second stage, by combining results obtained from each. Thus, in the first stage, missing values on a covariate of interest are replaced by imputed values using predictions from a model that uses a set of covariates deemed relevant to predict the variable of interest based on those

observations that were not missing. In the second stage, statistical regression methods are fitted to each of the imputed datasets and analysis results are integrated into a single, pooled result. The Multivariate Imputation via Chained Equations (MICE) R package[51] using predictive mean matching was used.[52]

The data collection tool on health-care resource use did not allow distinguishing between no consumption and missing reporting of consumption of health resources. However, given that resource use was collected by investigators in the study, true missingness was assumed negligible and hence no consumption of health resources was assumed where data was missing.

Estimating adjusted mean costs and quality-adjusted life years

Total costs and imputed QALYs were independently regressed on a set of baseline covariates, including treatment group and other potential predictor or treatment-effect modifiers that could be relevant for sub-group analyses. The variables defined for the trial's subgroup analyses (both the pre-specified set and the additional set) were also considered for inclusion here by the clinical advisors to the trial. The final set of covariates was:

- age (categorical, 1- 18-54; 2- 54-72; and 3- >72 years);
- gender (binary, 1- male; 0- female);
- body mass index (BMI, categorical, 1- 18.5-24.9; 2- 25.0-29.9; 3- 30.0-39.9; and 4- >=40 kg/m^2);
- mode of acquisition of infection (categorical, 1- community acquired; 2- nosocomial infection; and 3- healthcare associated);
- Charlson co-morbidity index score (categorical, 1- 0; 2- 1-2; 3- 3-4; and 5- >=5);
- neutrophil count (categorical, 1- <6; 2- 6-9; and >9 $10^9/L$);
- deep infection foci (binary, 1- yes; 0- no);
- endocarditis (binary, 1- yes; 0- no);
- methicillin-resistant *S. aureus* (MRSA, binary, 1- yes; 0- no);
- comatose (binary, 1- yes; 0- no); and
- randomised group.

Continuous variables were categorised using the same thresholds as used in subgroup analyses. In addition, baseline EQ-5D index score was used in the QALY regression as

patient's baseline utilities are likely to be highly correlated with their QALY estimates over the follow-up period, and thus, baseline utility imbalances need to be accounted for.[53]

Five scenarios were analysed: the first, a tentative scenario (models TC and TQ for total costs and QALYs, respectively), assessed the impact of randomised treatment alone in explaining the outcome variables; the second, the base-case, retained all covariates irrespective of their importance to explain the outcome (models 1C and 1Q for total costs and QALYs, respectively). The third scenario follows from the second, but retains/excludes covariates from the full covariate set to select the model of lowest Akaike Information Criteria (AIC).[54] The result is the most parsimonious model based on the AIC statistic, a measure of model quality and goodness of fit (models 1Cp and 1Qp for total costs and QALYs, respectively). A fourth scenario extends the base-case to include interactions with randomised treatment and explore treatment effect modifiers (models 2C and 2Q for total costs and QALYs, respectively). Finally, and similarly to scenario three, the most parsimonious interaction model based on the AIC statistic is obtained (models 2Cp and 2Qp for total costs and QALYs, respectively). The scenarios with and without randomised treatment interactions may have different implications for policy which will be examined.

Total QALYs and total costs captured during 84 days were regressed using a generalised linear modelling (GLM)[55] framework which accounts for the characteristics of the data (i.e. continuously distributed data potentially skewed). Alternative distributions and link functions were tested, and the best fitting based on Akaike's Information Criteria (AIC) was chosen.[54] To determine cost-effectiveness, predicted total costs and total QALYs were evaluated for the mean characteristics of all patients in the trial.

Note that the effect of randomised treatment was modelled independently for costs and health effects, although it is likely that some correlation exists. This should be considered in the interpretation of findings.

Cost-effectiveness and decision uncertainty

To ascertain the cost-effectiveness of a healthcare intervention relative to another, expected health benefits need to be considered against any additional costs expected to be incurred. The fact that a particular technology imposes additional costs means that other activities (that could be financed by these costs) are not undertaken, and this has health consequences to

other patients: the health opportunity costs. If the health gains associated with the technology compensate the health opportunity costs imposed by its additional costs, then using the technology brings net benefits to the NHS and could be recommended for use.

Health opportunity costs are often evaluated from the additional costs imposed by particular technologies using a cost-effectiveness threshold (lambda, λ). Currently the National Institute for Health and Care Excellence (NICE) sets the threshold at £20,000 to £30,000 per QALY gained (although recent work undertaken by the University of York has estimated this to be somehow lower – approximately £13,000 per QALY gained[56]). A new technology is considered cost-effective in relation to existing technologies if the net health benefit (NHB) is $NHB = \Delta B - \Delta C/\lambda > 0$, where λ, ΔB and ΔC represent, respectively, the cost-effectiveness threshold, the incremental benefits and incremental costs.

Decision makers may decide on the provision of services using expected cost-effectiveness findings. However, given the nature of the underlying evidence used, such expectation is not known with certainty. It is hence important that the consequences of uncertainty, and the extent to which it impacts on the adoption decision, are investigated to inform whether further research is needed.[57,58] Uncertainty here stems from the fact that all analyses being based on data collected within this trial, based on a sample of patients and hence generating uncertain estimates of population parameters. The cost-effectiveness analysis can, however, consider such uncertainty over expected costs and benefits (i.e. parameter uncertainty), and evaluate whether the decision to adopt (or reject) the technology is also uncertain i.e. if the Incremental Net Benefit (INB) crosses zero.

To propagate uncertainty in cost-effectiveness analyses, i.e. conduct a probabilistic analysis, Monte Carlo simulation methods are commonly used.[59] With a large number of simulations – in this work we have sampled 10,000 times – it is possible to examine the effect on costs, effects and hence on cost-effectiveness results when the underlying variables are allowed to vary simultaneously across a plausible range according to predefined distributions. Given total costs and benefits were modelled independently, their predicted distributions were also assumed independent. However, costs and benefits were individually modelled using a multivariate regression approach, and therefore to simulate the regression coefficients' variance-covariance matrix was considered in a multivariate Normal framework.[58]

Decisions that are uncertain have expected consequences to the NHS (as well as any attempt to delay or reverse it).[58,60] Acquiring more evidence to support the decision is expected to mitigate these risks, and hence quantifying the risks of uncertainty can inform the value of further evidence collection. The risks and consequences of uncertainty can be quantified using a simple extension of probabilistic analyses called expected value of perfect information (EVPI).[58] The EVPI determines the maximum amount the healthcare system should be willing to pay for more information. In the event the new evidence demonstrates the current decision to be wrong, the decision can be reversed benefiting prospective patients. Individual- and population-level EVPI estimates were estimated at the commonly used cost-effectiveness thresholds referred to above.

Subgroup analysis

Together with base-case and scenario analyses, which explored cost-effectiveness in the whole patient population with SAB, subgroup analyses were also implemented. Subgroup analyses are important as an intervention can prove to be cost-effective for one subgroup of the population and not for another. This might be because the baseline risk of events may differ or because treatment effects or cost implications are different across subgroups (i.e. treatment effect modifying factors). Thus, there may be population health gains from stratifying treatment decisions based on subgroup membership. These analyses explored subgroups based on the regression covariates, namely: age, mode of acquisition of infection, Charlson co-morbidity index score, BMI, deep infection foci, neutrophils and coma status.

Results

A total of 758 participants were recruited: 388 were randomly allocated to receive standard antibiotic therapy (placebo) and 370 to receive adjunctive rifampicin. Baseline characteristics of participants by treatment group can be found in **Table 12.** Note that one rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed. This patient has been excluded from all tables after baseline as they had no post-baseline data, leaving the number in the rifampicin group as 369 rather than 370 in the main Results section.

Resource use and costs

Table 13 provides summary statistics on the trial drug and all other antibiotic therapies received after randomisation during the trial active follow-up period. Fourteen patients (1.8%)

never initiated the trial drug. Active antibiotic therapies administered included flucloxacilin (n=597, 80.9%), ceftriaxone (n=164, 22.2%) and vancomycin (n=144, 19.5%). Open-label rifampicin was used in 52 (13.4%) and 32 (8.7%) patients in the placebo and rifampicin groups, respectively.

Table 12 Characteristics of study participants (health economic analyses)

Baseline characteristic, (n, %) **	Placebo (n=388)	Rifampicin (n=370)*	Total (n=758)*
Gender: male	246 (63.4%)	249 (67.3%)	495 (65.3%)
Age			
at last birthday (years) – mean (median, min-max)	63.0 (66.0, 20.0-100.0)	61.4 (64.0, 18.0-94.0)	62.2 (65.0, 18.0-100.0)
18 – 53 years	126 (32.5%)	125 (33.9%)	251 (33.2%)
54 – 71 years	126 (32.5%)	122 (33.1%)	248 (32.8%)
>= 72 years	136 (35.1%)	123 (33.3%)	259 (34.2%)
BMI			
in kg/m^2 – mean (median, min-max)	27.6 (26.4, 15.2-58.5)	27.2 (26.3, 12.1-73.6)	27.4 (26.3, 12.1-73.6)
< 18.4 kg/m^2	24 (6.2%)	21 (5.7%)	45 (5.9%)
18.5-24.9 kg/m^2	129 (33.2%)	128 (34.7%)	257 (33.9%)
25.0-29.9 kg/m^2	111 (28.6%)	113 (30.6%)	224 (29.6%)
30.0-39.9 kg/m^2	90 (23.2%)	77 (20.9%)	167 (22.1%)
>=40 kg/m^2	23 (5.9%)	21 (5.7%)	44 (5.8%)
Mode of acquisition of infection			
Community acquired	240 (61.9%)	245 (66.4%)	485 (64.1%)
Nosocomial infection (onset ≥48 hrs after admission)	76 (19.6%)	56 (15.2%)	132 (17.4%)
Healthcare associated (all other)	72 (18.6%)	68 (18.4%)	140 (18.5%)
Charlson comorbidity index score			
mean (median, min-max)	2.10 (2.00, 0.00-9.0)	1.97 (1.00, 0.00-11.0)	2.04 (2.00, 0.00-11.0)
0	117 (30.2%)	114 (30.9%)	231 (30.5%)
1-2	143 (36.9%)	154 (41.7%)	297 (39.2%)
3-4	74 (19.1%)	52 (14.1%)	126 (16.6%)
>=5	54 (13.9%)	49 (13.3%)	103 (13.6%)
Neutrophils (10^9/L)			
mean (median, min-max)	8.9 (7.30, 0.00-64.40)	9.25 (7.40, 0.00-83.70)	9.06 (7.30, 0.00-83.70)
<6	151 (38.9%)	135 (36.6%)	286 (37.8%)
6-9	95 (24.5%)	107 (29.0%)	202 (26.7%)
>9	137 (35.3%)	127 (34.4%)	264 (34.9%)
Methicilin resistance	21 (5.4%)	26 (7.0%)	47 (6.2%)
Deep infection foci	159 (41.0%)	142 (38.5%)	301 (39.8%)
Comatose status	43 (11.1%)	37 (10.0%)	80 (10.6%)
Endocarditis	18 (4.6%)	22 (6.0%)	40 (5.3%)

* One rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant. This participant is excluded from all other tables. **unless otherwise specified.

Table 13 Trial drug and active antibiotic therapies received from randomisation through to 84 days (trial active follow-up period), irrespective of dose, frequency and route of administration and indication (health economic analyses)

Patients n (%)	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Trial drug administration during active follow-up period			
n (%)	380 (97.9%)	364 (98.4%)	744 (98.3%)
Antibiotic therapy administration during active follow-up period			
Any antibiotic	382 (98.5%)	356 (96.5%)	738 (97.5%)
Flucloxacillin	315 (82.5%)	282 (79.2%)	597 (80.9%)
Ceftriaxone	81 (21.2%)	83 (23.3%)	164 (22.2%)
Vancomycin	79 (20.7%)	65 (18.3%)	144 (19.5%)
Piperacillin/tazobactam	62 (16.2%)	57 (16.0%)	119 (16.1%)
Gentamicin	45 (11.8%)	40 (11.2%)	85 (11.5%)
Rifampicin	52 (13.6%)	32 (9.0%)	84 (11.4%)
Teicoplanin	36 (9.4%)	41 (11.5%)	77 (10.4%)
Co-amoxiclavulante	46 (12%)	25 (7.0%)	71 (9.6%)
Meropenem	30 (7.9%)	24 (6.7%)	54 (7.3%)
Clindamycin	24 (6.3%)	29 (8.1%)	53 (7.2%)
Ciprofloxacin	29 (7.6%)	22 (6.2%)	51 (6.9%)
Metronidazole	24 (6.3%)	14 (3.9%)	38 (5.1%)
Daptomycin	13 (3.4%)	22 (6.2%)	35 (4.7%)
Doxycycline	16 (4.2%)	16 (4.5%)	32 (4.3%)
Linezolid	13 (3.4%)	12 (3.4%)	25 (3.4%)
Levofloxacin	12 (3.1%)	11 (3.1%)	23 (3.1%)
Trimethroprim	19 (5.0%)	1 (0.3%)	20 (2.7%)
Amoxicllin	10 (2.6%)	5 (1.4%)	15 (2.0%)
Other antibiotics*	67 (17.5%)	47 (13.2%)	114 (15.4%)

Note: Table 4 on 'Backbone' antibiotic treatment shows active 'backbone' antibiotics used to treat the bacteraemia, including antibiotics received before randomisation; numbers therefore differ to those shown here.

*Antibiotics with number of patients below 2% were combined in the "Other antibiotics" category but listed here for completeness: FusidicAcid (1.9%); Clarithromycin (1.8%); Cefuroxime (1.6%); Cotrimoxazole (1.6%); Amikacin (1.2%); Benzylpenicillin (0.9%); Erythromycin (0.9%); Nitrofurantoin (0.7%); Aztreonam (0.5%); Cefalexin (0.5%); Ertapenem (0.5%); Moxifloxacin (0.5%); Azithromycin (0.4%); Ceftazidime (0.4%); Phenoxymethylpenicillin (0.3%); Ticeracillin/clavulanate (0.3%); Tigecycline (0.3%); Cefadrine (0.1%); Cefotaxime (0.1%); Fidaxomicin (0.1%); Norfloxacin (0.1%); Ofloxacin (0.1%); PenicillinV (0.1%); and Temocilin (0.1%).

A summary of the secondary care health resources utilised during trial active follow-up period (i.e. from randomisation to 84 days of follow-up) is provided in **Table 14A**, and of consultations with healthcare providers in **Table 14B**.

All trial patients spent time in hospital, either in the ward or in a critical care unit, with a mean length of stay of 22.3 days post-randomisation (SD=19.7). Patients in the placebo group spent a mean 3.2 days more in the hospital ward than patients in the rifampicin group. Approximately 4% (n=33) of trial patients spent time in a critical care unit. Patients using these units had a mean stay of 11.0 days (SD=14.5). 177 (23%) patients were readmitted to hospital (as day case, to general ward or critical care unit) for any reason. Once readmitted to hospital to general ward or critical care unit, patients in both group spent a mean of 15 days

hospitalised (placebo group: mean 15.9 days, SD=19.0, n=92; rifampicin group: mean 13.9 days, SD=13.5, n=81). The number of hospital procedures and investigations undertaken were fairly balanced between treatment groups and across the different items. The most common hospital procedures were surgical drainage/removal of non-device related focus (n=74, 9.8%, with a mean of 1.3 (SD=0.8) per patient) and radiologically guided biopsy/aspirate/ abscess drainages (n=57, 7.5%, with a mean of 1.6 (SD=1.6) per patient). The most common hospital investigations included CT scans (n=273, 36.0%, with a mean of 1.8 (SD=1.8) per patient), ultrasound scans (other than echocardiogram) (n=237, 31.3%, with a mean of 1.7 (SD=1.1) per patient) and MRI scans (n=234, 30.9%, with a mean of 1.6 (SD=1.0) per patient). 316 (41.7%) trial patients had at least one hospital outpatient visit (**Table 14B**). 275 (36.3%) trial patients had a GP visit.

Table 14 Health resources utilised from randomisation through to 84 days (trial active follow-up period)

A Secondary care health resources

Secondary care health resource*		Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Hospital visits				
Total hospital stay from randomisation to first discharge **	mean (SD) days	23.9 (21.2)	20.5 (17.9)	22.3 (19.7)
Ward	mean (SD) days	23.4 (20.4)	20.2 (17.3)	21.8 (19.0)
	n patients (%)	388 (100.0%)	367 (99.5%)	755 (99.7%)
ITU	mean (SD) days	16.7 (20.9)	14.4 (10.6)	15.6 (16.4)
	n patients (%)	12 (3.1%)	11 (3.0%)	23 (3.0%)
HDU	mean (SD) days	1.8 (0.9)	1.3 (0.5)	1.5 (0.7)
	n patients (%)	4 (1.0%)	7 (1.9%)	11 (1.5%)
Total hospital readmissions	n patients (%)	94 (24.2%)	83 (22.5%)	177 (23.4%)
Hospital readmission (day case) ***	n patients (%)	4 (1.0%)	5 (1.4%)	9 (1.2%)
Hospital readmission (critical care) ***	n patients (%)	6 (1.5%)	4 (1.1%)	10 (1.3%)
Hospital readmission (ward) ***	n patients (%)	90 (23.2%)	80 (21.7%)	170 (22.5%)
Hospital readmission with overnight stay (in ward, ITU or HDU)	mean (SD) days	15.9 (19.0)	13.9 (13.5)	14.9 (16.7)
	n patients (%)	92 (23.7%)	81 (22.0%)	173 (22.9%)
Hospital procedures, including other				
Radiologically guided biopsy/ aspirate/ abscess	mean (SD)	1.4 (1.0)	1.7 (1.9)	1.6 (1.6)
	n patients (%)	25 (6.4%)	32 (8.7%)	57 (7.5%)
Surgical drainage/ removal of non-device related focus	mean (SD)	1.2 (0.4)	1.4 (1.1)	1.3 (0.8)
	n patients (%)	42 (10.8%)	32 (8.7%)	74 (9.8%)
Surgical removal of infected prosthetic device	mean (SD)	1.1 (0.4)	1.0 (0.0)	1.1 (0.2)
	n patients (%)	7 (1.8%)	8 (2.2%)	15 (2.0%)
Cardiac surgery for *S. aureus* endocarditis	mean (SD)	1.4 (0.9)	1.0 (0.0)	1.2 (0.6)
	n patients (%)	5 (1.3%)	6 (1.6%)	11 (1.5%)
Insertion of Hickman line	mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
	n patients (%)	5 (1.3%)	6 (1.6%)	11 (1.5%)

Secondary care health resource*		Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Other procedures	mean (SD)	1.53 (1.0)	1.45 (0.9)	1.49 (1.0)
	n patients (%)	78 (20.1%)	62 (16.8%)	140 (18.5%)
Hospital investigations, including other				
Ultrasound scan (other than echocardiogram)	mean (SD)	1.9 (1.1)	1.6 (1.1)	1.7 (1.1)
	n patients (%)	112 (28.9%)	125 (22.9%)	237 (31.3%)
CT scan	mean (SD)	1.9 (2.1)	1.73 (1.5)	1.83 (1.8)
	n patients (%)	145 (37.4%)	128 (34.7%)	273 (36.1%)
MRI scan	mean (SD)	1.7 (1.1)	1.6 (0.9)	1.7 (1.0)
	n patients (%)	127 (32.7%)	107 (29.0%)	234 (30.9%)
PET scan	mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
	n patients (%)	3 (0.8%)	4 (1.1%)	7 (0.9%)
PET CT scan	mean (SD)	1.1 (0.4)	1.0 (0.0)	1.1 (0.2)
	n patients (%)	7 (1.8%)	10 (2.7%)	17 (2.2%)
Bone scan	mean (SD)	1.0 (0.0)	1.3 (0.5)	1.13 (0.4)
	n patients (%)	9 (2.3%)	6 (1.6%)	15 (2.0%)
White cell scan	mean (SD)	2.0 (n/a)	n/a (n/a)	2.0 (n/a)
	n patients (%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other investigations	mean (SD)	2.5 (3.1)	2.1 (1.7)	2.3 (2.6)
	n patients (%)	31 (8.0%)	26 (7.0%)	57 (7.5%)

* note that summary statistics presented are restricted to the patients who experienced or were subject to interventions listed, e.g. 57 patients were subject to the 'Radiologically guided biopsy/ aspirate/ abscess' hospital procedure with a mean of 1.6 of these procedures per patient and 1.6 standard deviation; ** The mean (SD) time to hospital discharge (in days) from first hospital admission was estimated to be 20.68 (16.18) days. The total hospital stay (on first admission, in days), includes also cases where deaths or withdrawals happened before discharge (at their time of death or withdrawal respectively) and cases where the patient was not discharged at the end of the active follow-up period (duration taken as 84 days). Figure 3 and main Results show total days from admission to discharge, rather than from randomisation to discharge; *** Note that a patient may have had multiple readmissions, and these may have been different i.e. as day case, ward or critical care.

B Consultations with healthcare providers

Consultations with healthcare providers	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
All hospital outpatient visits within follow-up period			
Mean (SD)	4.6 (6.1)	4.6 (5.4)	4.6 (5.8)
n patients (%)	162 (41.8%)	154 (41.7%)	316 (41.7%)
All general practitioner visits within follow-up period			
Mean (SD)	2.9 (3.1)	3.1 (3.4)	3.0 (3.3)
n patients (%)	137 (35.3%)	138 (37.4%)	275 (36.3%)

* note that summary statistics presented are restricted to the patients who experienced the visits listed.

Total costs

Descriptive, unadjusted results

The unadjusted costs per category are shown in **Table 15.** The item with largest mean unadjusted cost was hospital stay in critical care on first admission (£14 625, SD=£20 272, n=34), followed by hospital stay in critical care on readmission (£9 034, SD=£8 036, n=10) and then by hospital procedures (£7 001, SD=£6 936, n=279).

For most categories, the mean unadjusted cost was fairly similar between treatment groups. However, and generally, mean unadjusted cost for hospital stay in the rifampicin group was

lower than in the placebo group. The mean unadjusted cost of hospital ward stay on first admission was greater (by approximately 16%) in the placebo group (£6 973, SD=£6 074, n=388) than in the rifampicin group (£6 025, SD=£5 165, n=367, as two participants allocated to rifampicin were only ever on ITU/HDU). Similarly, mean unadjusted costs relating to hospital stay in critical care was also higher in the placebo group compared to the rifampicin group – although fewer than 5% (n=34) of trial patients were admitted to hospital in these circumstances.

Mainly driven by greater hospital stay, the unadjusted total cost over the active follow-up period for the placebo group was estimated to be mean £1 364 higher than in the rifampicin group (placebo group: £12 861, SD=£12 753 *vs* rifampicin: £11 498, SD=£10 116).

Table 15 Unadjusted costs during trial active follow-up period*

Unadjusted cost (£) *		**Placebo (n=388)**	**Rifampicin (n=369)**	**Total (n=757)**
Treatment costs				
Trial drug **	mean (SD)	£0.0	£30.7 (59.4)	n/a (n/a)
	n patients (%)	380 (97.9%)	364 (98.4%)	744 (98.3%)
All antibiotic therapy	mean (SD)	£862.1 (1 841.8)	£836.0 (1 114.5)	£849.2 (1 525.8)
	n patients (%)	351 (90.5%)	342 (92.7%)	693 (91.5%)
Secondary care health resources utilised				
Hospital first admission				
Hospital ward stay	mean (SD)	£6 973.2 (6 073.4)	£6 025.4 (5 164.6)	£6 512.5 (5 666.1)
	n patients (%)	388 (100.0%)	367 (99.5%)	755 (99.7%)
Hospital stay in critical care (ITU or HDU)	mean (SD)	£17 241.3 (25 719.7)	£12 299.0 (14 209.8)	£14 624.8 (20 272.4)
	n patients (%)	16 (4.1%)	18 (4.9%)	34 (4.5%)
Hospital readmission				
Hospital ward stay	mean (SD)	£4 680.8 (5 659.4)	£4 092.0 (4 038.6)	£4 403.7 (4 957.6)
	n patients (%)	90 (23.2%)	80 (21.7%)	170 (22.5%)
Hospital stay in critical care (ITU or HDU)	mean (SD)	£9 472.5 (9 556.2)	£8 375.3 (6 367.6)	£9 033.6 (8 035.6)
	n patients (%)	6 (1.5%)	4 (1.1%)	10 (1.3%)
Day case	mean (SD)	£481.3 (192.5)	£385.1 (0)	£427.9 (128.4)
	n patients (%)	4 (1.0%)	5 (1.4%)	9 (1.2%)
Hospital procedures	mean (SD)	£7 079.4 (6 810.4)	£6 920.0 (7 088.4)	£7 001.1 (6 936.2)
	n patients (%)	142 (36.6%)	137 (37.1%)	279 (36.9%)
Hospital investigations	mean (SD)	£423.0 (449.2)	£367.9 (398.5)	£395.6 (425.2)
	n patients (%)	249 (64.2%)	246 (66.7%)	495 (65.4%)
Consultations with healthcare providers				
Hospital outpatient visits	mean (SD)	£624.6 (833.4)	£626.1 (734.8)	£625.3 (785.6)
	n patients (%)	162 (41.8%)	154 (41.7%)	316 (41.7%)
General practitioner visits	mean (SD)	£104.3 (111.6)	£110.1 (123.1)	£107.2 (117.3)
	n patients (%)	137 (35.3%)	138 (37.4%)	275 (36.3%)
Total costs over the follow-up period	mean (SD)	£12 861.3 (12 753.1)	£11 497.8 (10 116.0)	£12 196.6 (11 555.7)
	n patients (%)	388 (100.0%)	369 (100.0%)	757 (100.0%)

* These statistics are based on available cases, i.e. missing responses were assumed to be zero when there was at least one non-missing response; ** Placebo was assumed to be of £0 cost.

Unadjusted costs per treatment group are, alternatively, presented by time intervals in **Table 16.** As some healthcare resource consumption within the active follow-up period had no associated date, either because assessment date or form date was not available, the mean unadjusted costs of unspecified date are also presented.

During the first 2 weeks after randomisation, similar estimated costs were observed between treatment groups with mean unadjusted costs of approximately £5 880 and £6 293, respectively for rifampicin and placebo groups. During the following 10 weeks and until the end of active follow-up, the healthcare allocated to the placebo group was estimated to cost mean £787 more than the care required by patients in the rifampicin group (rifampicin: £4 524 *vs* placebo: £5 311). Similarly, unadjusted mean costs of healthcare during active follow-up period but of no specified date were higher in the placebo group relative to the rifampicin group.

Table 16 Unadjusted costs by time period*

Unadjusted cost (£)	**Placebo (n=388)**	**Rifampicin (n=369)**	**Total (n=757)**
From baseline to day 14			
Mean (SD)	£6 293.1 (8 259.3)	£5 879.7 (7 606.4)	£6 088.6 (7 945.2)
n patients (%)	380 (97.9%)	369 (100.0%)	749 (98.9%)
Days 15 to 84			
Mean (SD)	£5 310.5 (8 574.3)	£4 523.8 (6 855.7)	£4 927.0 (7 789.0)
n patients (%)	285 (73.5%)	247 (66.9%)	532 (70.3%)
*Day unspecified, within follow-up period***			
Mean (SD)	£2 130.9 (4 643.7)	£1 952.1 (3 661.9)	£2 045.8 (4 201.3)
n patients (%)	192 (49.5%)	169 (45.8%)	361 (47.7%)

* These statistics are based on available cases, i.e. missing responses were assumed to be zero when there was at least one non-missing response; ** Day unspecified implies that a date of assessment or CRF date was not available.

Adjusted results

Base-case model (model 1C)

A series of distributional and functional assumptions were modelled. Models assuming observed data followed a gamma distribution with a log link function produced the lowest AIC statistics (highlighted in bold) for the different scenarios (**Table 33** in **Appendix 2**). Note that smaller AIC values indicate better model quality of fit. Thus, for the base-case (model 1C) and the treatment interactions model (model 2C) a gamma distribution with a log link function was chosen.

The results of the regression models TC and 1C are presented in **Table 17.** Additionally, the results of model 1Cp, the most parsimonious model based on AIC using the covariate set of model 1C, are also presented.

Results showed that no evidence exists that indicate that healthcare costs differed between the rifampicin and placebo groups (p-value=0.14 in model 1C). Note that, given the non-linear specification of the model, coefficients are interpreted multiplicatively rather than additively. Thus, and for instance, to obtain predicted total costs with model 1C we have that, a patient at the reference category for all factors is associated with expected costs of £8 752 [calculated as *exp(9.08)*]. For the rifampicin group, total expected costs are £7 956 [calculated as *exp(-0.10+9.08)= exp(9.08)*exp(-0.10)*= £8 752 * 0.91].

Patients with nosocomial infections, with deep foci infection, with endocarditis, with neutrophils count above $6x10^9$/L and in a coma had significantly higher healthcare costs than those in the respective reference categories (community-acquired infections, without deep foci, without endocarditis, with neutrophils $<6x10^9$/L, with consciousness, respectively). Model 1Cp retained only the above mentioned variables, reinforcing that this reduced covariate set is sufficient to explain variation in healthcare resource consumption.

Table 17 Modelling total costs over the active follow-up period (84 days) – base-case and parsimonious model results

Model specification	**Model TC**	**Model 1C**	**Model 1Cp**
Type of regression model		Gamma, log link	
Equation		Log Total costs	
Covariates (baseline)	coefficient [SE]	coefficient [SE]	coefficient [SE]
Randomised treatment (1-rifampicin; 0-placebo)	-0.11 [0.07]	-0.10 [0.07]	---
Age, 54-71 years	---	0.08 [0.08]	---
Age, >=72 years	---	0.04 [0.08]	---
Gender (1-male;0-female)	---	-0.06 [0.07]	---
Acquisition, nosocomial infection	---	0.35 [0.09] ***	0.37 [0.09] ***
Acquisition, healthcare associated	---	0.06 [0.09]	0.07 [0.09]
Charlson index, 1-2	---	0.11 [0.08]	---
Charlson index, 3-4	---	0.01 [0.11]	---
Charlson index, >=5	---	0.06 [0.11]	---
BMI, 18.5-24.9 kg/m^2	---	-0.23 [0.14]	---
BMI, 25.0-29.9 kg/m^2	---	-0.09 [0.15]	---
BMI, 30.0-39.9 kg/m^2	---	-0.14 [0.15]	---
BMI, >=40 kg/m^2	---	-0.11 [0.19]	---
Deep focus (1-yes; 0-no)	---	0.36 [0.07] ***	0.35 [0.07] ***
Endocarditis (1-yes; 0-no)	---	0.50 [0.15] **	0.43 [0.16] **
Methicilin resistance	---	0.18 [0.14]	---
Neutrophils, 6-9 10^9/L	---	0.12 [0.08]	0.09 [0.08]
Neutrophils, >9 10^9/L	---	0.30 [0.08] ***	0.29 [0.08] ***
Comatose (1-yes; 0-no)	---	0.28 [0.11] *	0.27 [0.11] *
Intercept	9.46 [0.05] ***	9.08 [0.16] ***	8.97 [0.07] ***
Observations	757	730	730

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1.

Model 1C predictions can be found in **Table 18,** first set of results. For the mean patient in the trial (**Table 12**) across all covariates used in the regression, the weighted mean predicted total cost for the placebo group was £1 092 higher than in the rifampicin group (rifampicin: £11 050, SE=£510 *vs* placebo: £12 142, SE=£546). Model 1Cp total cost predictions were similar, in magnitude, to model 1C.

Table 18 Predicted total costs over the follow-up period by treatment group

Cost predictions (£)	Model	Placebo	Rifampicin
Mean predicted total costs [95% CI]	Model 1C	£12 142 [£11 194, £13 249]	£11 050 [£10 089, £12 068]
Median predicted total costs [interquartile range]		£12 129 [£11 778 – £12 500]	£11 040 [£10 708 – £11 389]
Mean predicted total cost difference [95% CI]		-£1 092 [-£2 564, -£371.7]	
Mean predicted total costs [95% CI]	Model 2C	£11 969 [£10 962, £13 040]	£10 900 [£9 947, £11 925]
Median predicted total costs [interquartile range]		£11 952 [£11 604 – £12 321]	£10 889 [£10 556 – £11 233]
Mean predicted total cost difference [95% CI]		-£1 068 [-£2 510, £392]	

Scenario analysis – consideration of treatment effect modifiers (model 2C)

Results of model 2C can be found in **Table 19** Results of modelling total costs over the active follow-up period (84 days) – exploring treatment effect modifiers through treatment interactions model and a parsimonious interaction model**.** The scenario analysis using a model with treatment interactions (model 2C), irrespective of their statistical significance, showed that, in general, the associations observed in model 1C persisted. Note that the BMI category of 18.5 to 24.9 kg/m^2 was now associated with lower healthcare costs relative to the reference BMI category (<18.5 kg/m^2). The predicted total costs for a patient at the reference category for all other factors in the rifampicin group in model 2C are: *exp(-0.43+9.23)*= £6 635, while for the placebo group: *exp(9.23)*= £10 240.

Model 2Cp restricted model 2C to the covariates and potential effect modifiers that represent the most parsimonious model. Results for this model are also shown in **Table 19** Results of modelling total costs over the active follow-up period (84 days) – exploring treatment effect modifiers through treatment interactions model and a parsimonious interaction model**.** This model produced similar findings to the model 1Cp, with the exception that age and randomised treatment interaction with age were now retained. Patients in the rifampicin group

and in the age category between 54 and 71 years of age were associated with higher healthcare costs (£8 602, calculated as *exp(9.00-0.16-0.05+0.27)*] than those in the placebo group (£7 726, calculated as *exp(9.00-0.05)*]). The predicted total costs for a patient at the reference category for all other factors in the rifampicin group in model 2Cp was: *exp(9.00-0.16)*= £6 908, while for the placebo group: *exp(9.00)*= £8 128.

Model 2C weighted total cost predictions considering the mean patient in the trial across all covariates can be found in **Table 18.** Overall, total cost predictions are similar to the ones obtained in model 1C, the base case model. Model 2Cp total cost predictions (not shown) for the placebo group were £1 239 higher than in the rifampicin group. Total cost predictions for each patient subgroup and randomised treatment are presented in the cost-effectiveness and decision uncertainty section.

Table 19 Results of modelling total costs over the active follow-up period (84 days) – exploring treatment effect modifiers through treatment interactions model and a parsimonious interaction model

Model specification	**Model 2C**	**Model 2Cp**
Type of regression model	Gamma, log link	
Equation	Log Total costs	
Covariates (baseline)	coefficient [SE]	coefficient [SE]
Randomised treatment (1-rifampicin; 0-placebo)	-0.43 [0.31]	-0.16 [0.11]
Age, 54-71 years	-0.05 [0.11]	-0.05 [0.12]
Age, >=72 years	0.05 [0.12]	0.08 [0.11]
Gender (1-male;0-female)	-0.12 [0.09]	---
Acquisition, nosocomial infection	0.38 [0.12] **	0.36 [0.09] ***
Acquisition, healthcare associated	0.11 [0.12]	0.09 [0.09]
Charlson index, 1-2	0.13 [0.11]	---
Charlson index, 3-4	0.02 [0.14]	---
Charlson index, >=5	0.25 [0.15] .	---
BMI, 18.5-24.9 kg/m^2	-0.41 [0.20] *	---
BMI, 25.0-29.9 kg/m^2	-0.35 [0.20] .	---
BMI, 30.0-39.9 kg/m^2	-0.28 [0.20]	---
BMI, >=40 kg/m^2	-0.41 [0.26]	---
Deep focus (1-yes; 0-no)	0.49 [0.10] ***	0.33 [0.07] ***
Endocarditis (1-yes; 0-no)	0.43 [0.22] .	0.48 [0.16] **
Methicillin resistance	0.22 [0.21]	---
Neutrophils, 6-9 10^9/L	0.15 [0.12]	0.09 [0.08]
Neutrophils, >9 10^9/L	0.30 [0.11] **	0.29 [0.08] ***
Comatose (1-yes; 0-no)	0.16 [0.15]	0.25 [0.11] *
Treatment * Age, 54-71 years	0.25 [0.16] .	0.27 [0.16] .
Treatment * Age, >=72 years	-0.05 [0.17]	-0.06 [0.16]
Treatment * Gender (1-male;0-female)	0.11 [0.14]	---
Treatment * Acquisition, nosocomial infection	-0.06 [0.18]	---
Treatment * Acquisition, healthcare associated	-0.06 [0.18]	---
Treatment * Charlson index, 1-2	-0.06 [0.16]	---
Treatment * Charlson index, 3-4	0.005 [0.21]	---
Treatment * Charlson index, >=5	-0.36 [0.21] .	---
Treatment * BMI, 18.5-24.9 kg/m^2	0.37 [0.28]	---
Treatment * BMI, 25.0-29.9 kg/m^2	0.51 [0.29]	---
Treatment * BMI, 30.0-39.9 kg/m^2	0.27 [0.30] .	---

Model specification	Model 2C	Model 2Cp
Treatment * BMI, >=40 kg/m^2	0.61 [0.37]	---
Treatment * Deep focus (1-yes; 0-no)	-0.25 [0.14] .	---
Treatment * Endocarditis (1-yes; 0-no)	0.19 [0.31]	---
Treatment * Methicillin resistance	-0.10 [0.28]	---
Treatment * Neutrophils, 6-9 10^9/L	-0.04 [0.16]	---
Treatment * Neutrophils, >9 10^9/L	0.02 [0.15]	---
Treatment * Comatose (1-yes; 0-no)	0.17 [0.22]	---
Intercept	9.23 [0.22] ***	9.00 [0.10] ***
AIC	15 105	15 080
Observations	730	730

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1.

Health benefits

Utility and quality-adjusted life-years (unadjusted and not using multiple imputation)

At baseline, there were approximately 10% (n=80) comatose patients and 3% (n=20) of patients unable or unwilling to provide answers to the EQ-5D questionnaire due to their poor health. Descriptive statistics on HRQoL at different assessment times can be found in **Table 20A.** Observed EQ-5D scores by domain/level and by time period can be found in **Table 34** in **Appendix 2**.

Table 20 Unadjusted EQ-5D index scores and QALYs by treatment group

A. Unadjusted EQ-5D index scores over time

Unadjusted EQ-5D index score *	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Baseline			
n patients (%)	381 (98.2%)	365 (98.9%)	746 (98.5%)
- Number responded	329 (84.8%)	317 (85.7%)	646 (85.2%)
- Number in coma	43 (11.1%)	37 (10.0%)	80 (10.5%)
- Number unwilling/unable	9 (2.3%)	11 (3.0%)	20 (2.6%)
Mean of unadjusted EQ-5D index score (SD) *	0.09 (0.35)	0.12 (0.34)	0.10 (0.34)
Day 7			
n patients (%)	314 (80.9%)	293 (79.4%)	608 (80.3%)
- Number responded	283 (72.9%)	258 (69.9%)	542 (71.6%)
- Number in coma	24 (6.2%)	24 (6.5%)	48 (6.3%)
- Number unwilling/unable	7 (1.8%)	11 (3.0%)	18 (2.4%)
- Number died	7 (1.8%)	13 (3.5%)	20 (2.6%)
Mean of unadjusted EQ-5D index score (SD) *	0.19 (0.34)	0.19 (0.35)	0.19 (0.34)
Day 14			
n patients (%)	240 (61.9%)	213 (57.7%)	453 (59.8%)
- Number responded	215 (55.4%)	188 (50.9%)	403 (53.2%)
- Number in coma	20 (5.2%)	18 (4.9%)	38 (5.0%)
- Number unwilling/unable	5 (1.3%)	7 (1.9%)	12 (1.6%)
- Number died	17 (4.4%)	25 (6.8%)	42 (5.5%)
Mean of unadjusted EQ-5D index score (SD) *	0.20 (0.34)	0.17 (0.32)	0.19 (0.33)
Day 84			
n patients (%)	280 (72.2%)	251 (68.0%)	531 (70.1%)
- Number responded	273 (70.4%)	244 (66.1%)	516 (68.2%)
- Number in coma	2 (0.5%)	2 (0.5%)	4 (0.5%)

- Number unwilling/unable	5 (1.5%)	5 (1.4%)	10 (1.5%)
- Number died	56 (14.4%)	56 (15.2%)	112 (14.8%)
Mean of unadjusted EQ-5D index score (SD) *	0.29 (0.31)	0.32 (0.28)	0.30 (0.29)

*Deceased patients received an EQ-5D index score of *0*; Comatose patients received an EQ-5D index score of *-0.402*; Patients reported to be unable/unwilling to provide EQ-5D answers received an EQ-5D index score of *-0.261*, corresponding to the bottom decile of the EQ-5D index score distribution of all trial patients for which a EQ-5D index score was available.
** Deceased patients, in a coma or unable/unwilling to provide EQ-5D answers were allocated scores as described in footnote *.

B Unadjusted total QALYs (not using multiple imputation, but including hard imputations for coma/unwilling/unable to complete and death)

Unadjusted total QALYs	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Mean (SD)	0.054 (0.063)	0.059 (0.059)	0.057 (0.061)
n patients (%)	275 (70.9)	249 (67.3)	524 (69.1)

Descriptive statistics of the EQ-5D index scores (unadjusted) show that the mean score is fairly balanced across treatment groups, irrespective of time point of assessment. The baseline unadjusted mean EQ-5D index score was 0.10 (SD=0.34, n=746), reflecting the very poor quality of life of patients affected with *S. aureus* bacteraemia. At 7 days the unadjusted mean EQ-5D index score was 0.19 (SD=0.34, n=608) and at 14 days also 0.19 (SD=0.33, n=453). At this assessment point, 42 (5.5%) patients had died and hence were allocated an EQ-5D index score of *0*. In interpreting these figures, care is needed as 40% fewer patients completed the EQ-5D questionnaire at 14 days. At the end of the active follow-up (84 days) the mean unadjusted EQ-5D index score was 0.30 (SD=0.29, n=531). Again, at this point 112 (14.8%) of patients were deceased and received an EQ-5D index score of *0*. Although only about 70% (n=531, including values allocated for deceased/comatose/unable to answer patients as per Methods, denoted "hard" imputations below) of the total number of patients that were recruited into the trial completed an EQ-5D at 84 days, it shows that the selective group of patients for whom a EQ-5D index score at 84 days was obtained had a better (higher) mean EQ5D score than the remaining individuals, at baseline. Distributions of EQ-5D index score at baseline, 7, 14 and 84 days (not using multiple imputation, but including hard imputations for coma/unwilling/unable to complete and death) are shown in **Figure 22** in **Appendix 4**.

The unadjusted total QALYs (over the whole of the follow-up period, including hard imputed values as per Methods) are presented in **Table 20B.** We highlight again that results correspond to only about 70% of the sample as information for remaining patients was missing. Given that the period of assessment is 84 days (i.e. 3 months = a quarter of a year), the maximum total QALYs that we can observe is 0.25. Thus, the distribution of total QALYs

will be inherently be both left and right truncated. Mean unadjusted total QALYs were similar between treatment groups, with a total mean QALY of 0.06 (SE=0.06). The distribution of total unadjusted total QALYs, including hard imputed values as per Methods, can be seen in **Figure 19A**.

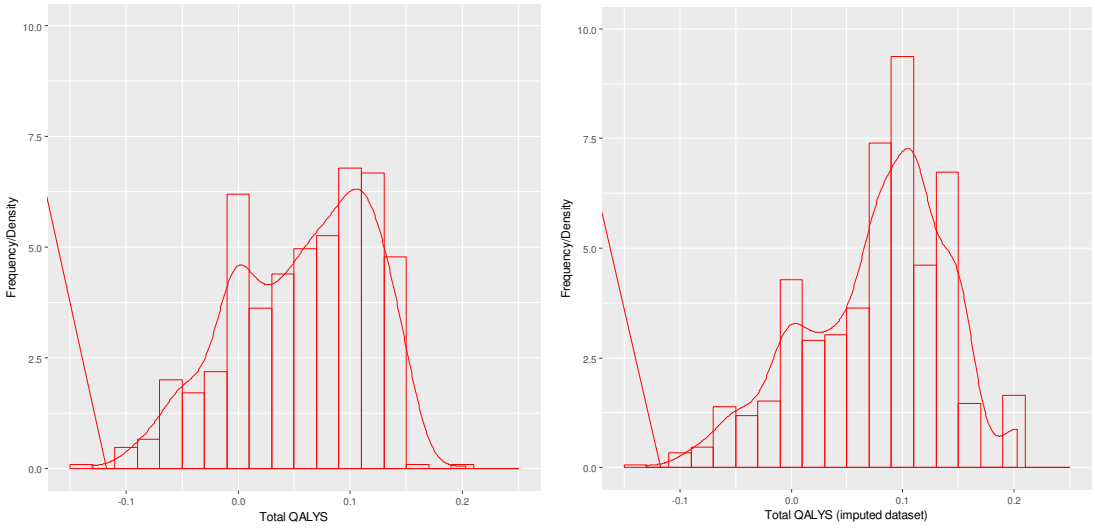


Figure 19 A. Distribution of total QALYs; and B. Distribution of imputed total QALYs from one randomly selected imputed dataset using multiple imputation techniques

Quality-adjusted life-years (using multiple imputation)

A multiple imputation procedure was used to impute missing total QALYs at 84 days, which occurred in approximately 31% of the sample. Following suggestion from the literature in which the number of imputations should be similar to the percentage of cases that are incomplete,[61,62] 30 imputations of 20 iterations each were performed. Mode of acquisition of infection, Charlson co-morbidity index score, BMI, deep infection foci, endocarditis, neutrophil count, coma status and EQ-5D index score were the baseline patient characteristics used as predictors by the imputation model. This process generated 30 different datasets with a calculated imputed outcome variable (i.e. total QALYs at 84 days). The distribution of total QALYs at 84 days for one of the imputed datasets, randomly chosen, can be seen in **Figure 19B**. On these multiple imputed datasets, alternative GLM models for the total QALYs at 84 days were considered. As for the cost data, the null model, a model only with randomised treatment (model TQ) and a model with all covariates were implemented (model 1Q). A regression model assuming a normally distributed outcome with identity link (i.e. ordinary least squares model) was chosen (AIC statistic in model 1Q: -2 109). Other modelling distributional assumption tested either did not run or did not converge.

Base-case model (model 1Q)

The results of the base case model (model 1Q) are shown in **Table 21.** These results are complemented with results of the model considering randomised treatment only (model TQ, first column). Regression models presented are linear and therefore additive, so coefficients can be interpreted directly to assess their impact on the outcome variable. In the model 1Q, being randomised to rifampicin was associated with slightly higher total QALYs (mean 0.004, SE=0.004) than being randomised to placebo, although this association was not statistically significant (p=0.40, similar for model TQ). As expected, the EQ-5D index score at baseline was one of the main predictors of total QALYs accrued over 84 days, with one unit higher baseline EQ-5D estimated to be associated with higher total QALYs (model 1Q: mean difference of 0.06, 95% CI 0.05 to 0.08). Conversely, those of 72 years or older (model 1Q: -0.043, 95% CI -0.072 to -0.014), having any co-morbidities as indicated in the Charlson co-morbidity index (gradient from -0.015, 95% CI -0.027 to -0.003 for index scores of 1-2, up to -0.024, 95% CI -0.041 to -0.006, for higher index scores) and being in a coma (-0.020, 95% CI -0.037 to -0.004) was associated with significantly lower total QALYs. These covariates, together with methicillin resistance and neutrophil count, were retained in model 1Qp, showing that the latter are also relevant to explain variation in total QALYs.

Table 21 Modelling total QALYs at end of active follow-up period (84 days) using multiple imputation – base-case and parsimonious model results

Model specification	**Model TQ**	**Model 1Q**	**Model 1Qp** [+]
Type of regression model	OLS		
Equation	Total QALYs (imputed)		
Covariates (baseline)	coefficient [SE]	coefficient [SE]	coefficient [SE]
EQ-5D index baseline score	---	0.064 [0.008] ***	0.064 [0.008] ***
Randomised treatment (1-rifampicin; 0-placebo)	0.007 [0.005]	0.004 [0.004]	---
Age, 54-71 years	---	-0.026 [0.020]	-0.027 [0.020] ***
Age, >=72 years	---	-0.043 [0.014] **	-0.044 [0.014] **
Gender (1-male;0-female)	---	0.004 [0.005]	---
Acquisition, nosocomial infection	---	-0.005 [0.006]	---
Acquisition, healthcare associated	---	-0.001 [0.006]	---
Charlson index, 1-2	---	-0.015 [0.006] **	-0.015 [0.006] *
Charlson index, 3-4	---	-0.019 [0.008] **	-0.020 [0.007] **
Charlson index, >=5	---	-0.024 [0.009] **	-0.024 [0.009] **
BMI, 18.5-24.9 kg/m^2	---	0.005 [0.010]	---
BMI, 25.0-29.9 kg/m^2	---	0.005 [0.010]	---
BMI, 30.0-39.9 kg/m^2	---	0.010 [0.011]	---
BMI, >=40 kg/m^2	---	0.004 [0.013]	---
Deep focus (1-yes; 0-no)	---	0.0004 [0.005]	---
Endocarditis (1-yes; 0-no)	---	0.003 [0.011]	---
Methicilin resistance	---	-0.027 [0.020]	-0.024 [0.021]
Neutrophils, 6-9 10^9/L	---	0.004 [0.006]	0.005 [0.006]
Neutrophils, >9 10^9/L	---	-0.010 [0.006] .	-0.011 [0.006] .
Comatose (1-yes; 0-no)	---	-0.020 [0.008] *	-0.020 [0.008] *

Intercept	0.076 [0.009] ***	0.104 [0.012] ***	0.115 [0.006] ***
Observations	757	724	724

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1. + 30 parsimonious models were obtained, one for each imputed dataset. The covariate set retained in the parsimonious models was slightly different across models. Thus, results shown use a majority rule, i.e. when the covariate was retained 3 or more times.

For the mean patient in the trial across all covariates used in the regression, the weighted mean predicted total QALYs for the placebo group was similar in the rifampicin and the placebo groups (**Table 22,** first set of results). As expected, due to model linearity, the difference in predicted total QALYs between treatment groups was estimated to be mean 0.004 (SE=0.004). Results of the sensitivity analysis on patients unable/unwilling to provide EQ-5D answers can be found in **Tables 35, 36 and 37** in **Appendix 2**.

Table 22 Predicted total QALYS at the end of the active follow-up period by treatment group (using multiple imputation)

HRQoL predictions (QALYS)	Model	Placebo	Rifampicin
Mean predicted total QALYs [SE]	Model 1Q	0.077 [0.008]	0.080 [0.009]
Median predicted total QALYs [interquartile range]		0.077 [0.071 – 0.082]	0.080 [0.074 – 0.086]
Mean predicted total QALYs difference		0.004 [0.004]	
Mean predicted total QALYs [SE]	Model 2Q	0.076 [0.010]	0.080 [0.013]
Median predicted total QALYs [interquartile range]		0.076 [0.070 – 0.083]	0.080 [0.071 – 0.088]
Mean predicted total QALYs difference		0.004 [0.003]	

Scenario analysis – consideration of treatment effect modifiers (model 2Q)

As for total costs, a scenario analysis was implemented for total QALYs (model 2Q) considering treatment interactions. The results of this scenario analysis can be found in **Table 23.** In general, similar results to model 1Q were obtained. Following model 1Q, model 2Q did not find treatment to be significantly associated with total QALYs. Model 2Qp results (also in **Table 23)** show that the most parsimonious model retained the following covariates as important to explain the outcome variable: EQ-5D baseline score, age, Charlson index, methicillin resistance, neutrophil count and coma status. Thus, randomised treatment and randomised treatment interactions were not selected for the most parsimonious model based on AIC statistics. As for model 1Q, and considering the mean trial patient, as no statistically significant difference was found between treatment groups, both groups had similar mean total QALYs (**Table 22,** second set of results). Total QALYs predictions for each patient subgroup and randomised treatment are presented in the cost-effectiveness and decision uncertainty section.

Table 23 Modelling total QALYs at end of follow-up period (multiple imputation)

Model specification	**Model 2Q**	**Model 2Qp**
Type of regression model	OLS	
Equation	Total QALYs (imputed)	
Covariates (baseline)	coefficient [SE]	coefficient [SE]
EQ-5D index score	0.064 [0.011] ***	0.064 [0.008] ***
Randomised treatment (1-rifampicin; 0-placebo)	0.016 [0.022]	---
Age, 54-71 years	-0.028 [0.020]	-0.027 [0.020]
Age, >=72 years	-0.041 [0.014] **	-0.044 [0.014] **
Gender (1-male;0-female)	0.005 [0.007]	---
Acquisition, nosocomial infection	-0.002 [0.008]	---
Acquisition, healthcare associated	-0.005 [0.009]	---
Charlson index, 1-2	-0.011 [0.008]	-0.015 [0.006] *
Charlson index, 3-4	-0.017 [0.010] .	-0.020 [0.007] **
Charlson index, >=5	-0.012 [0.010]	-0.024 [0.009] **
BMI, 18.5-24.9 kg/m^2	-0.0003 [0.014]	---
BMI, 25.0-29.9 kg/m^2	0.004 [0.014]	---
BMI, 30.0-39.9 kg/m^2	0.015 [0.014]	---
BMI, >=40 kg/m^2	0.015 [0.018]	---
Deep focus (1-yes; 0-no)	0.008 [0.007]	---
Endocarditis (1-yes; 0-no)	-0.005 [0.016]	---
Methicillin resistance	-0.020 [0.028]	-0.024 [0.021]
Neutrophils, 6-9 10^9/L	0.010 [0.009]	0.005 [0.006]
Neutrophils, >9 10^9/L	-0.018 [0.008] *	-0.011 [0.006] .
Comatose (1-yes; 0-no)	-0.020 [0.012] .	-0.020 [0.008] *
Treatment * EQ-5D index score	0.003 [0.016]	---
Treatment * Age, 54-71 years	0.005 [0.011]	---
Treatment * Age, >=72 years	-0.007 [0.011]	---
Treatment * Gender (1-male;0-female)	-0.003 [0.009]	---
Treatment * Acquisition, nosocomial infection	-0.010 [0.012]	---
Treatment * Acquisition, healthcare associated	0.008 [0.013]	---
Treatment * Charlson index, 1-2	-0.007 [0.011]	---
Treatment * Charlson index, 3-4	-0.003 [0.016]	---
Treatment * Charlson index, >=5	-0.024 [0.016]	---
Treatment * BMI, 18.5-24.9 kg/m^2	0.009 [0.020]	---
Treatment * BMI, 25.0-29.9 kg/m^2	0.003 [0.020]	---
Treatment * BMI, 30.0-39.9 kg/m^2	-0.009 [0.021]	---
Treatment * BMI, >=40 kg/m^2	-0.020 [0.026]	---
Treatment * Deep focus (1-yes; 0-no)	-0.018 [0.011] .	---
Treatment * Endocarditis (1-yes; 0-no)	0.019 [0.021]	---
Treatment * Methicillin resistance	-0.013 [0.022]	---
Treatment * Neutrophils, 6-9 10^9/L	-0.007 [0.011]	---
Treatment * Neutrophils, >9 10^9/L	0.015 [0.011]	---
Treatment * Comatose (1-yes; 0-no)	-0.001 [0.017]	---
Intercept	0.098 [0.015] ***	0.115 [0.006] ***
Observations	724	724

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1. + 30 parsimonious models were obtained, one for each imputed dataset. The covariate set retained in the parsimonious models was slightly different across models. Thus, results shown use a majority rule, i.e. when the covariate was retained 3 or more times.

Cost-effectiveness and decision uncertainty

The results presented above on the analysis of costs and health outcomes (QALYs) showed that participants randomised to receive rifampicin for the treatment of *S. aureus* bacteraemia were expected to attain higher QALYs over the duration of the trial, and were expected to

incur lower costs than those participants allocated to receive placebo. These results were not, however, statistically significant.

Considering the mean total costs and mean total QALYs at face value, adjunctive rifampicin could promote relevant cost savings over an 84-day time horizon without compromising health outcomes, and that actually there may be even positive, although small, implications to total QALYs (**Table 24**). This means that rifampicin dominates placebo, that is, it costs less but provides additional health benefits compared to placebo. If releasing £20 000 to the NHS is assumed to result in 1 additional QALY (the cost-effectiveness threshold), the mean incremental net health benefit (INHB) of adjunctive rifampicin is approximately 0.06 QALY (SE=0.04 QALY).

Table 24 Cost-effectiveness – base-case and scenario analysis results

Cost-effectiveness outcomes – mean [SE]		**Placebo**	**Rifampicin**
Base case results (using results from regression models 1C and 1Q)			
Predicted total costs (£)		£12 142 [546.0]	£11 050 [509.7]
Predicted total QALYs		0.077 [0.008]	0.080 [0.009]
Incremental predicted total costs (£)		-£1 092 [749.8]	
Incremental predicted total QALYs		0.004 [0.004]	
ICER (£/QALY gained)		Rifampicin dominates, i.e. costs less and has positive health benefits in relation to placebo	
Incremental net health benefit *	£13 000/QALY	0.088 [0.058]	
	£20 000/QALY	0.058 [0.038]	
	£30 000/QALY	0.040 [0.025]	
Probability of being cost-effective *	£13 000/QALY	0.07	0.93
	£20 000/QALY	0.06	0.94
	£30 000/QALY	0.06	0.94
Scenario analysis results (using results from regression models 2C and 2Q)			
Predicted total costs (£)		£11 969 [535.8]	£10 900 [500.2]
Predicted total QALYs		0.076 [0.010]	0.080 [0.013]
Incremental predicted total costs (£)		-£1 068 [726.6]	
Incremental predicted total QALYs		0.004 [0.003]	
ICER (£/QALY gained)		Rifampicin dominates, i.e. costs less and has positive health benefits in relation to placebo	
Incremental net health benefit *	£13 000/QALY	0.086 [0.056]	
	£20 000/QALY	0.057 [0.037]	
	£30 000/QALY	0.039 [0.024]	
Probability of being cost-effectiveness *	£13 000/QALY	0.06	0.94
	£20 000/QALY	0.06	0.94
	£30 000/QALY	0.06	0.94

* at cost-effectiveness thresholds of £13 000, £20 000 and £30 000 per QALY gained, respectively.

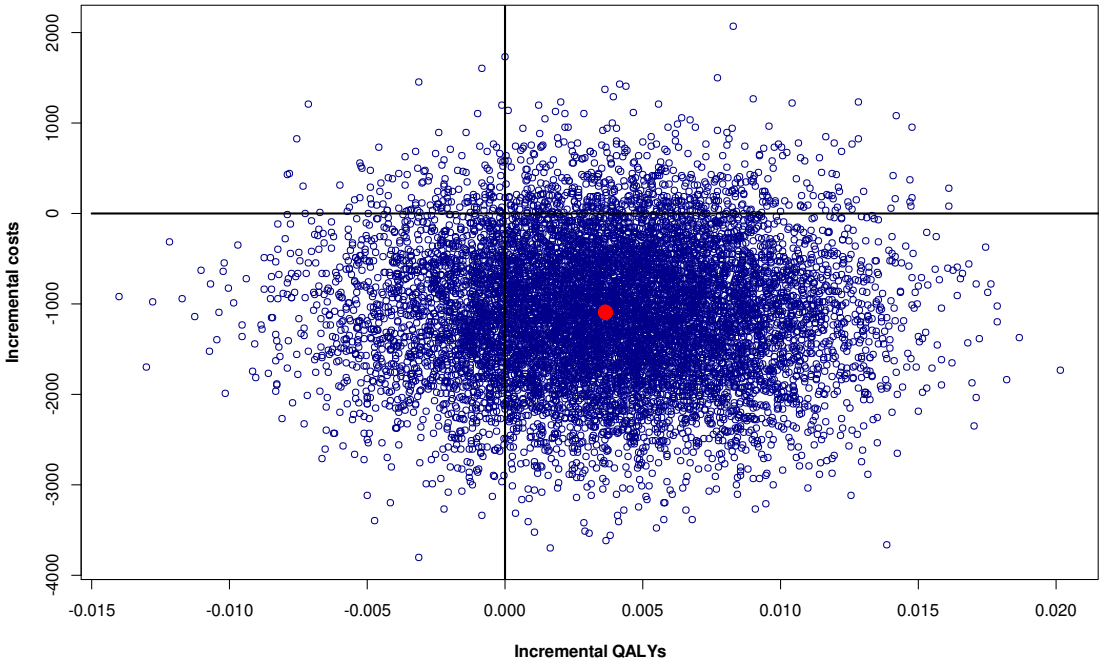


Figure 20 Cost-effectiveness plane for the base case results

Figure 20 shows the cost-effectiveness plane using results from the Monte Carlo simulation to represent uncertainty over incremental mean costs and QALYs (joint density plot). Each blue dot represents a simulated incremental cost and QALY pair; the cloud of blue points is representative of the uncertainty around the cost-effectiveness outcomes. The red dot displays the mean incremental costs and effects. The majority of blue points lay in the 4th quadrant of negative incremental costs and positive incremental benefits. The ARREST trial data shows rifampicin is likely to be less costly and is associated with small QALY gains (although uncertain) in the 84 days of follow-up (post-randomisation). This suggests rifampicin is cost-effective with very little associated uncertainty, i.e. a very high probability of being cost-effective (93-94%). Similar results to the base-case were found for the scenario analysis (**Table 24**).

Considering a technology time horizon of 10 years and an annual effective population of 12,500 patients per year in the UK [1], the expected value of perfect information (EVPI) for the MRSA/MSSA bacteraemia population is estimated to be approximately £2 million at the commonly used cost-effectiveness thresholds. This estimate represents the maximum amount the healthcare system should be willing to pay for further information and resolve identified uncertainties. At the individual-level and for the same cost-effectiveness threshold values, the EVPI is estimated to be approximately £20 per MRSA/MSSA patient.

Subgroup-analysis

This subgroup analysis uses the exploratory models with interactions (models 2C and 2Q) presented above to evaluate the evidence of ARREST on whether costs and QALY impacts of an *S. aureus* episode differ with patient characteristics, and to evaluate whether there are subgroups where the cost-effectiveness profile of rifampicin differs.

In terms of the costs of an *S. aureus* episode, the results of this analysis (**Table 25**) suggests that patients presenting with a nosocomial infection, low BMI, deep infection foci, endocarditis and MRSA have higher episode costs (above £15000 per episode) than their counterparts. In what concerns QALYs, high neutrophil count (>9 10^9/L), MRSA or older than 72 years of age at presentation were factors associated with lower overall QALYs. With respect to the impact of baseline patient characteristics on the cost-effectiveness of rifampicin, the subgroup analysis suggests that, for most subgroups rifampicin offers net health gains in relation to placebo. Those where rifampicin may not offer net health gains in relation to placebo are: age group between 54 and 72 years, BMI between 25.0-29.9 kg/m^2 and above 40 kg/m^2, endocarditis and coma. Note that this analysis is exploratory and findings should be interpreted with care.

Table 25 Cost-effectiveness results by treatment group and for a range of baseline characteristics considering the base-case scenario

Cost-effectiveness outcomes by subgroups *	Placebo (mean [SE])		Rifampicin (mean [SE])		INHB**	PCE Rifampicin ***
	Costs	QALYs	Incr. Costs	Incr.		
Age						
Age: 18-54 years	£11 991 [975]	0.099 [0.006]	-£1 773 [1 287]	0.004 [0.006]	0.092	0.93
Age: 54-72 years	£11 364 [918]	0.071 [0.021]	£1 135 [1 360]	0.009 [0.009]	-0.047	0.25
Age: > 72 years	£12 637 [1 013]	0.059 [0.014]	-£2 388 [1 316]	-0.002 [0.009]	0.117	0.96
Gender						
Female	£12 958 [984]	0.073 [0.011]	-£1 944 [1 315]	0.006 [0.005]	0.102	0.94
Male	£11 492 [651]	0.078 [0.010]	-£634 [885]	0.002 [0.005]	0.034	0.78
Mode of acquisition of infection						
Community acquired	£10 998 [640]	0.078 [0.011]	-£767 [869]	0.004 [0.004]	0.041	0.83
Nosocomial infection	£16 066 [1 665]	0.075 [0.012]	-£1 970 [2 373]	-0.006 [0.011]	0.094	0.78
Healthcare associated	£12 291 [1 317]	0.072 [0.011]	-£1 499 [1 764]	0.012 [0.012]	0.087	0.83
Charlson co-morbidity index score						
Score 0	£10 989 [924]	0.085 [0.011]	-£233 [1 312]	0.010 [0.009]	0.020	0.62
Score 1-2	£12 517 [909]	0.074 [0.010]	-£1 014 [1 213]	0.003 [0.007]	0.054	0.81
Score 3-4	£11 225 [1 215]	0.068 [0.013]	-£147 [1 880]	0.007 [0.013]	0.013	0.56
Score >5	£14 089 [1 700]	0.073 [0.015]	-£4 414 [2 084]	-0.013 [0.011]	0.209	0.98
BMI						
<18.5 kg/m^2	£17 016 [3 153]	0.071 [0.018]	-£6 471 [3 739]	0.003 [0.021]	0.322	0.97
18.5-24.9 kg/m^2	£11 179 [860]	0.070 [0.009]	-£1 072 [1 175]	0.012 [0.008]	0.066	0.87
25.0-29.9 kg/m^2	£11 826 [982]	0.075 [0.011]	£393 [1 414]	0.006 [0.007]	-0.015	0.42

30.0-39.9 kg/m^2	£12 723 [1 169]	0.086 [0.011]	-£2 378 [1 560]	-0.006 [0.008]	0.113	0.93
>=40 kg/m^2	£11 222 [2 098]	0.085 [0.021]	£1 645 [3 255]	-0.017 [0.019]	-0.099	0.27
Deep infection foci						
No	£9 855 [605]	0.073 [0.010]	£56 [850]	0.011 [0.005]	0.007	0.57
Yes	£16 111 [1 148]	0.081 [0.011]	-£3 479 [1 513]	-0.007 [0.005]	0.167	0.99
Endocarditis						
No	£11 703 [537]	0.076 [0.010]	-£1 153 [730]	0.003 [0.003]	0.060	0.95
Yes	£18 325 [4 080]	0.071 [0.016]	£1 654 [5 768]	0.022 [0.023]	-0.056	0.42
Methicillin resistance						
No	£11 805 [540]	0.077 [0.011]	-£984 [741]	0.004 [0.004]	0.053	0.92
Yes	£15 029 [3 083]	0.058 [0.028]	-£2 669 [3 780]	-0.009 [0.021]	0.127	0.75
Neutrophil count						
<6 10^9/L	£10 998 [640]	0.078 [0.011]	-£767 [869]	0.004 [0.004]	0.041	0.83
6-9 10^9/L	£12 824 [1 707]	0.087 [0.017]	-£1 404 [2 208]	-0.004 [0.011]	0.065	0.72
>9 10^9/L	£14 944 [1 793]	0.060 [0.010]	-£769 [2 513]	0.019 [0.010]	0.055	0.67
Coma						
No	£11 769 [558]	0.078 [0.010]	-£1 245 [751]	0.004 [0.004]	0.066	0.96
Yes	£13 945 [2 002]	0.058 [0.014]	£899 [2 975]	0.003 [0.015]	-0.043	0.39

* mean characteristics across the whole sample was used to estimate subgroup results; ** INHB: Incremental Net Health Benefit at £20,000 cost-effectiveness threshold; *** PCE Rifampicin: Probability that Rifampicin is cost-effective vs Placebo at £20,000 cost-effectiveness threshold

Discussion

The ARREST trial aimed to determine whether or not adjunctive rifampicin improved outcomes following *S. aureus* bacteraemia, but found no evidence of an effect either on resolution of bacteraemia or on mortality (design and effectiveness results of the trial are reported in detail in Chapters 3 and 4, respectively). In this chapter we first focused on evaluating the cost and HRQoL implications of *S. aureus* bacteraemia using the trial data.

This first set of analyses found that an episode of *S. aureus* bacteraemia costs, on average, £12 197 over 12 weeks (unadjusted results). The cost categories that contribute the most to costs (descriptive analyses) are length of stay (primary hospital admission and readmissions) and procedures undertaken in hospital. Determinants of higher episode costs (variables evaluated at baseline), evident from the trial population, were: whether the primary infection was nosocomial (episode costs 41% higher); deep focus primary infection (episode costs 43% higher); endocarditis (episode costs 65% higher), high neutrophil count (>9 10^9/L, episode costs 34% higher), and if the patient was comatose (episode costs 33% higher). For example, for an infection classified as having a *deep foci* the mean costs of the episode were estimated at £12 514, whilst for infections without a *deep focus* the mean costs were £8 752. In the ARREST population, neither age, gender, BMI, Charlson index nor methicillin resistance were found to determine costs at standard levels of standard statistical significance.

Analysis indicate that adjunctive rifampicin may save 10% of episode costs, although this result was not statistically significant at the standard 95% level (p=0.14). Descriptive, unadjusted, analyses suggest that these savings start in the first 14 days of treatment (unadjusted difference in the first 14 days was £413), but that are perhaps most relevant after 14 days (unadjusted difference of £787). Because the trial was not powered on this outcome, the relevance of this finding (had a larger sample size been recruited) is unclear. However, this result is consistent with the reduction in recurrences, which occurred in a small proportion of participants, but significantly fewer in the rifampicin group (1% vs 4% placebo).

As expected in this population of acutely ill patients, very low values of the EQ5D score were observed at baseline (mean EQ-5D score of 0.10). A high proportion of patients were comatose, and a high proportion of individuals had health states that the valuation algorithm ascribes as worse than death (i.e. returning negative EQ5D score values). Unadjusted figures show, however, that mean HRQoL score was significantly higher at 84 days (mean 0.30). The measure of benefit in the adjusted analysis considered QALYs over 84 days. QALYs are often the recommended measure of benefit for societal decision-makers, as they are generic and thus allow comparisons to be made across different treatments, conditions and patient populations. Give the high mortality and the low HRQoL that this population is subjected to, total QALYs over the 84 days were on average 0.077 per patient, only 33% of the maximum innings for this period (0.23 QALY or 84/365). Determinants of QALYs in the sample were: baseline EQ5D score (0.0064 QALYs lost for every 0.1 decrease in baseline EQ-5D); higher age (up to 0.044 QALY loss); Charlson index (up to 0.024 QALY loss) and comatose (mean QALY loss of 0.020). As opposed to total costs, deep foci infection did not affect total QALYs. After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (SE=0.004 QALY). Given the lack of statistical significance, the relevance of the finding that rifampicin has a positive (but small) effect on total QALYs is unclear; however, it is in accordance with the reduction in recurrences in the rifampicin group.

Public Health England conducts mandatory enhanced surveillance of MRSA bacteraemia since October 2005 and of MSSA bacteraemia since January 2011. From April 2017 to March 2017 823 cases of MRSA and 11 486 cases of MSSA were reported in England.[1] At the

episode cost determined in ARREST, these incidence figures imply a £150 million burden to the NHS.

Based on the analyses from ARREST, adjunctive rifampicin could result in 'cost' savings and negligibly small gains in mean QALYs. The cost-savings possibly arise from reductions in hospital stay and readmissions in the short term. In cost-effectiveness terms, adjunctive rifampicin could be said to dominate placebo. Our within-trial economic analysis, however, excluded potentially important outcomes, such as resistance arising from increased use of rifampicin and the clinical consequences of its drug-drug interactions (which may not have been captured fully in our analyses as costs of non-antibiotic drugs were not included, nor were costs of monitoring tests, e.g. for toxicity). This was a pragmatic decision because patients enrolled in this trial had wide range of underlying conditions and will have required a very large number of other drugs. A decision was therefore made not to try record all these other drugs on CRFs, making them impossible to cost. Similarly it was difficult to know what quantitative data to record to assess drug interactions – rather than collect a large amount of free text to try to code, and risk missing different items for different episodes, a pragmatic decision was made to not include these on CRFs either. Moreover, the ARREST trial was conducted under experimental conditions and, despite providing unbiased estimates of treatment effects, practice may not be as homogeneous and hence further research could confirm whether any predicted cost-savings would be effectively realised in practice.

Chapter 6 Discussion

We conducted a large, multi-centre, pragmatic, placebo-controlled trial which randomised 758 adults with *S. aureus* bacteraemia. Our trial was designed to determine whether rifampicin, added to standard 'backbone' antibiotics for up to 14 days, reduced bacteriologically-confirmed failure or recurrence or death by 12-weeks. We found no evidence that rifampicin affected any of the composite primary or secondary efficacy measures including mortality, the duration of bacteraemia, or the development of rifampicin-resistant *S. aureus.* Rifampicin was, however, associated with a small but significant reduction in bacteriologically and clinically-defined disease recurrences.

The population included in the trial represents the severity and heterogeneity of *S. aureus* bacteraemia. Participants were mostly older adults (median age 65 years), many with a number of co-morbidities (median Charlson score 2). A substantial minority (9.2%) were enrolled in an intensive care unit, reflecting the severity of the infection. Substantial improvements in hospital infection prevention and control over the last decade in the UK meant that most (64.0%) infections were acquired in the community, with only 17.4% being nosocomial in origin (acquired more than 48 hours after hospital admission). Similarly, the UK has witnessed a major decline in MRSA infections over the same period and only 6.2% of patients had bacteraemia caused by MRSA.[63] A deep infection focus, denoting a complicated infection, was present at baseline in 301 (39.7%), around half with endocarditis, orthopaedic or intravascular devices, or osteoarticular infections, and 139 (18.3%) had no established infection focus. Therefore a substantial proportion of patients had what are generally as considered as uncomplicated infections, in which there is a single, superficial, and easily removable infection focus (an infected intravascular catheter, for example) without evidence of deep infection foci.

One of the key findings from the trial is the enormous variation in the choice and duration of 'backbone' antibiotics (**Table 26** in **Appendix 2**). The majority (81.7%), however, received flucloxacillin (an anti-staphylococcal penicillin) at some point in their primary treatment. In the United Kingdom and Australia, flucloxacillin is the recommended first-line anti-staphylococcal penicillin for MSSA infections; whereas other agents, such as nafcillin and cloxacillin, are recommended in the United States. There is no evidence supporting clinically

relevant differential anti-staphylococcal activity between these antibiotics,[64,65] and we therefore believe our results are generalisable across countries regardless of their chosen anti-staphylococcal penicillin. 50.1% of patients received a glycopeptide at some point in their primary treatment, likely reflecting ongoing concerns about MRSA infections despite the overall low rates, particularly given the severity of disease in many of the trial participants. The use of other antibiotics (including open-label rifampicin) and the total duration of active antibiotic therapy (median 29 days) were similar between randomised groups. Fewer rifampicin than placebo treated participants were restarted on antibiotics after the primary treatment course, which may reflect the lower recurrence rate in the placebo group. The variety of antibiotics received demonstrates the utter infeasibility of conducting a trial restricting to one single backbone antibiotic. Further, had we used only one standard antibiotic regimen, clinicians could legitimately argue that the effect of rifampicin might be different on another backbone antibiotic. All antibiotic regimens were chosen by infection specialists taking into account individual patient allergy and concomitant medication. We found no evidence of variation in the lack of effect of rifampicin by initial treatment class. We therefore consider that the results are more generalizable than would have been obtained from one single regimen.

Planned subgroup analysis did not identify a sub-population of participants who clearly benefited from the addition of rifampicin. There was a suggestion that rifampicin's effect may have varied according to antibiotics used at randomisation, with any benefit restricted to those with MSSA infection treated with flucloxacillin alone. However, this result has uncertain clinical significance. There was no evidence of benefit if flucloxacillin was used with vancomycin or another antibiotic, or if antibiotic class was used to define subgroups, findings that are inconsistent with an isolated effect of flucloxacillin. With 20 subgroups analysed, one statistically significant association may have occurred by chance. Many infection specialists might have predicted that rifampicin might benefit those with deep, complicated infection the most, and possibly those with disease caused by MRSA. We could find no such associations, although only a small minority of participants had MRSA bacteraemia. Indeed, if anything those with MRSA bacteraemia did worse with rifampicin than placebo (**Figure 5(b)**).

We hypothesised that the early addition of rifampicin to standard antibiotic treatment would enhance the early killing of *S. aureus* and thereby improve outcomes. The trial inclusion criteria therefore required rifampicin to be initiated anywhere from 0-96 hours after initiating

active antibiotics for the infection. Given most patients with *S. aureus* bacteraemia are very unwell and require immediate empirical antibiotic therapy, and it takes at least 36 hours to culture and identify *S. aureus* from blood cultures, it is unsurprising that participants received a median of 62 hours of other active antibiotics before treatment with rifampicin. This may have represented a clinically meaningful delay in initiating rifampicin treatment which could have affected efficacy. However, there was no evidence of such an effect considering time from randomisation to initiation of rifampicin/placebo as either categorical subgroups or as a continuous interaction factor (**Figure 5(b)**). Additional sub-group analysis needs to be interpreted carefully, given the number of tests performed[66] and we do not believe they should be highlighted as clinically significant findings within the conclusions of the study.

We believe that the study results refute the hypothesis that adjunctive rifampicin enhances *S. aureus* killing in blood and thereby reduces the risk of dissemination and death.[15] Both randomised groups had similar rates of bacterial clearance in blood, and there was no evidence of difference in all-cause mortality over the short (2 weeks), medium (12 weeks) or even in the longer-term (>52 weeks). Even the 50% of deaths that were adjudicated as definitely/probably due to *S. aureus* (50%) occurred similarly in rifampicin and placebo groups. However, the observed mortality in our trial was lower than that observed in many recent observational studies. For example, a recent large multi-centre case-series reported substantially higher 12-week mortality (29.2%)[67] than we observed (14.8%). The few randomised controlled trials that have been reported in this disease (the trial of daptomycin in *S. aureus* bacteraemia,[68] for example) tend to report lower mortality. This probably reflects differences in the populations between observational and interventional studies. It is possible that the most severely unwell patients, who are expected to die quickly, are less likely to enter interventional studies. Indeed, in ARREST there were 129 patients who either died or were considered too unwell for active treatment and therefore did not join the trial (**Figure 2**). Mortality would have nearly doubled had they joined the trial and died. But there may be other reasons for the lower mortality observed in the ARREST trial. Regular infection specialist consults were also mandatory for the trial, which may have reduced mortality. Infection consults have been associated with improved *S. aureus* bacteraemia outcomes in observational studies.[69]

Another hypothesis, that rifampicin enhances the sterilisation of deep infection foci and thus reduces disease recurrences, is, at least partially, supported by our findings.[70] We found a

small but statistically significant reduction in recurrences in the rifampicin group, suggesting some biological activity of the drug. However, the clinical significance of such a small reduction is unclear. The numbers-needed-to-treat to prevent bacteriologically and clinically-defined recurrences were 29 and 26 respectively. More importantly, prevention of recurrences did not affect either short-term or long-term mortality (**Figure 9, Figure 10**). Of note, the independent, blinded endpoint review committee adjudicated that recurrences were much more likely to have been caused by failure to recognise or remove the primary infection focus than by failure antibiotic treatment (**Table 7**). This observation demonstrates the importance of source management in future research to improve outcomes from *S. aureus* bacteraemia. Recent strategies that enhance the identification of infection foci by positron emission tomography (PET) scanning have been associated with reduced mortality from *S. aureus* bacteraemia.[71] Taken together, these findings suggest the need for a multifaceted approach to improving outcomes from *S. aureus* bacteraemia. Rifampicin may assist in sterilising deep *S. aureus* infection foci and prevent a few recurrences, but it does not replace the need to define and, when possible, drain or remove the infection focus.

The modest benefit of rifampicin on recurrences (and any resulting cost savings) needs to be balanced against the toxicity of rifampicin and complications surrounding its use, especially in an older population with co-morbidities, often requiring other drug treatments. Predicted drug interactions or pre-existing liver disease prevented 306/2896 (10.6%) screened subjects from being randomised. Whilst there was no evidence of differences between groups in the proportions with SAEs, significantly more antibiotic-modifying AEs and drug-interactions occurred in rifampicin participants. AEs were predominantly gastrointestinal disorders and, interestingly, renal impairment. Rifampicin was associated with acute kidney injury in 17 participants, compared with 6 placebo participants. Although the numbers are small, and renal impairment is a recognised toxicity of rifampicin in the Summary of Product Characteristics, this is an important aspect of its use which is rarely considered by clinicians. In contrast, drug-induced liver injury was predicted to be common but turned out to be extremely rare, possibly because patients vulnerable to liver injury were not enrolled.

The strengths of the ARREST trial include its placebo-controlled, multi-centre and pragmatic design. This ensures it provides generalisable, clinically relevant findings to clinicians and patients within the NHS. It is also the largest trial ever conducted examining *S. aureus* bacteraemia treatment. It does, however, have important limitations that reflect the many

challenges of performing trials in acutely unwell patients with severe bacterial infections and in the current UK trial funding arena.[72] The heterogeneous nature of this severe disease, and the requirement to randomise patients within 96 hours of the start of antibiotic therapy because of the underlying hypothesis, led to a large number of ineligible patients and meant recruitment was slower than anticipated. Only 26.6% (770/2896) of those screened were enrolled; the most common reason was having already received >96 hours of antibiotics, in around one-third of those not enrolled (664 (31.2%). Furthermore, 232 (10.9%) screened subjects were not randomised because rifampicin was considered mandatory. This information was available only as a reason for ineligibility with no additional details, but anecdotally prosthetic device-related infections were common in these patients. Rifampicin's clinical effect may potentially have been reduced as a consequence of excluding these patients, reducing the findings' relevance to those with bacteraemia associated with infected prostheses, where rifampicin may have more benefit.[33]

A proportion of patients initiated open-label rifampicin or stopped blinded trial drug early, predominantly for drug-drug interactions or AEs. Such deviation from intended treatment would be expected in normal clinical practice, and therefore the intention-to-treat comparison of the groups likely reflects the effectiveness of rifampicin more widely. There was however also no evidence of benefit from rifampicin in the per-protocol population who received ≥80% of expected doses. Outcome ascertainment was very high, with only a small number (~9%) of patients in whom vital status and/or signs and symptoms could not be ascertained at the 12 week follow-up visit. The total number randomised in error and lost-to-follow-up or withdrawing consent was very close to the 10% incorporated in the sample size calculation.

A far more critical limitation to timely completion of this trial was the heterogeneity in the trials support network in the UK, which is far more suited to recruiting large numbers of chronically unwell individuals from a small number of fixed clinics, than recruiting acutely unwell individuals who present sporadically at varying times of day and night and require a great deal of care in explaining research at a time of acute illness. Some centres received excellent support and were able to recruit larger numbers. Others received, for example, research nurse support on two fixed days of the week, regardless of when patients presented acutely unwell, or were unable to access promised support when patients did present, because research staff were committed to fixed clinics at the time. Thus in many centres the burden of recruiting patients and conducting research visits fell to the PI, typically a consultant

microbiologist or infection specialist who took this on outside their day-to-day work. There are clearly enormous challenges for research networks in supporting trials in acute, relatively uncommon, sporadic, diseases – but their severity, with one in six patients dying in this trial - highlights the importance of finding a way to do this. Even more frustrating was the system of "targets", which are extremely difficult to assess in acute illnesses such as *S. aureus* bacteraemia. One of the top recruiting sites was forced to close to recruitment early, despite the trial struggling as a whole to meet its recruitment targets, because their individual site target had been met and the local research office was required to move its resources to other studies to avoid being penalised. The unintended consequences of rigid adherence to targets, which are really impossible to specify with any degree of confidence in acutely presenting complaints such as *S. aureus* bacteraemia, was an increase in the total time the trial took to recruit. Particularly when randomised controlled trials are competing with observational studies for research support, there needs to be a better way to encourage sites that are able to recruit to trials to do so beyond arbitrary targets.

Originally, the trial was powered to detect an absolute difference of 10% in bacteriological failure/recurrence or death from 35% to 25% **and** a 7% absolute reduction in mortality from 16% to 9%, based on results from a small systematic review.[73] Slow recruitment meant that the mortality co-primary endpoint was moved to a secondary endpoint, consequently reducing the sample size needed to detect the 10% absolute reduction in bacteriological failure/recurrence or death because the two-sided alpha (false positive) increased from 0.025 (two co-primary outcomes) to 0.05 (one primary outcome). The 758 eligible participants included are more than double the number in the largest previous trial in *S. aureus* bacteraemia,[24] and increase the total numbers with *S. aureus* bacteraemia recruited in randomised trials over the last 50 years by 50%. The 95% CI around our estimates of the difference between rifampicin and placebo lie within 7.5%, smaller than the 10% non-inferiority margins recommended by licencing authorities for antibiotic trials and commonly used in other infections such as HIV. This would have been considered to conclusively demonstrate non-inferiority of rifampicin had we used an active comparator. Although the trial was designed to test the superiority of rifampicin, it thus provides convincing evidence of non-inferiority of rifampicin to placebo; that is, convincing evidence of lack of benefit. A small minority (13%) used open-label rifampicin in the placebo group, but per-protocol analyses confirmed this well-estimated lack of benefit of rifampicin over placebo.

We found that an episode of *S. aureus* bacteraemia costs, on average, £12 197 over 12 weeks. These costs were driven primarily by length of stay and procedures undertaken in hospital. Last year (April 2016 to March 2017) there were 12 309 episodes of *S. aureus* bacteraemia reported within the NHS in England.[74] We therefore estimate *S. aureus* costs the NHS around £150 million each year.

Interventions that reduced these costs would be welcome. On the basis of the clinical data provided by the trial we concluded that rifampicin was of no overall clinical benefit to individuals with *S. aureus* bacteraemia. However, our cost effectiveness analysis suggested adjunctive rifampicin may have a possible health economic benefit to the NHS. Rifampicin was estimated to save 10% of episode costs (p=0.14). Most of these savings related to small reductions in length of hospital stay, especially after the first 14 days of treatment. These reductions probably relate to the small but significant reductions on recurrences associated with the use of rifampicin over placebo (1% vs 4%; p=0.01).

Important limitations to the cost-effectiveness analysis include the missing costs of rifampicin toxicity (including monitoring for toxicity) and drug-drug interactions in the analysis. These important clinical complications of rifampicin treatment were highlighted in the clinical data but were not captured in the cost effectiveness analysis. In addition, the widespread use of rifampicin would undoubtedly lead to the increased prevalence of rifampicin resistance amongst *S. aureus* and other medically important bacteria. These costs could be substantial, especially if it caused a rise in rifampicin-resistant *Mycobacterium tuberculosis* infections, and have not been considered. In short, on balance, we do not believe that the possible cost savings of rifampicin to the NHS should outweigh the lack of overall clinical benefit to an individual with *S. aureus* bacteraemia. In support of this position is the lack of a significant effect of rifampicin on QALYs.

The ARREST trial was developed with the assistance of the Healthcare-associated Infection Service Users Research Forum and Jennifer Bostock, our PPI representative. Ms Bostock advised on the inclusion of incapacitated adults and the application of the Mental Capacity Act, and the information provided to patients. The information sheets, consent forms and recruitment processes were developed in collaboration with the SURF and Ms Bostock to help ensure that they communicated the risks and benefits clearly and appropriately. There were sensitive ethical issues which arose at ethical review and the PPI representative was

instrumental in helping the team gain ethical approval. Furthermore, when it was necessary for the trial team to request an extension to the study from the funders Ms Bostock accompanied them to the meeting and helped put the case as to why the trial was important to patients/relatives and the public. The panel remarked that it was the first time they had seen a public member attend such a meeting. It reflected the trial team's commitment to PPI and the creative use to which they engaged the 'expertise' of Ms Bostock. Ms Bostock was also a member of the ARREST Trial Steering Committee.

It was Ms Bostock's idea to run a qualitative sub-study within the main trial (see Chapter 4). The study was designed, developed and delivered by her with assistance from the trial team. It was deemed important that the PPI representative was responsible for this aspect of the trial as it was felt that there would be a better response rate and more honest answers if the person conducting the study was independent and had a 'public voice'. The sub-study was small in scope and had limited findings; however it was an unusual inclusion in a trial of this nature.

PPI played, and will continue to play, an active role in disseminating the trial's results. Ms Bostock has both reviewed and co-authored some of the main academic outputs from the study and the main conference presentations of the results, as well as a leaflet presenting results to patients and their GPs (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1010425/#/). It is important to the entire trial team that dissemination goes beyond the traditional academic and healthcare professional communities to others, patient groups and the wider public. With this in mind the team agreed that having a creative approach to dissemination to engage with patients, the public and policy makers may benefit this process. An example of this creative approach is provided by an Infographic, designed by Will Everett (Science Communications Officer at the MRC CTU at UCL), which summarises the trial's findings for dissemination (**Figure 21**). This was reviewed and revised by the PPI advisor and will be used to showcase the trial and results to patients and the public after publication. In addition, Ms Bostock and other members of the trial team were interviewed for a PodCast aimed at clinicians (please go to: https://soundcloud.com/user-110325996-105034477/arrest-podcast-v03/s-J4lta). The interviewees discussed the results of the study and their implications for healthcare workers and patients and the public. Ms Bostock and her wider network will continue to disseminate the results of the study to relevant audiences via her links with MRSA Action UK, The Healthcare Infection Society, The Infection Prevention Society, The Patients Association, The

Research Design Service PPI Advisory Group and The Biomedical Research Centre (GSTT) PPI Advisory Group.

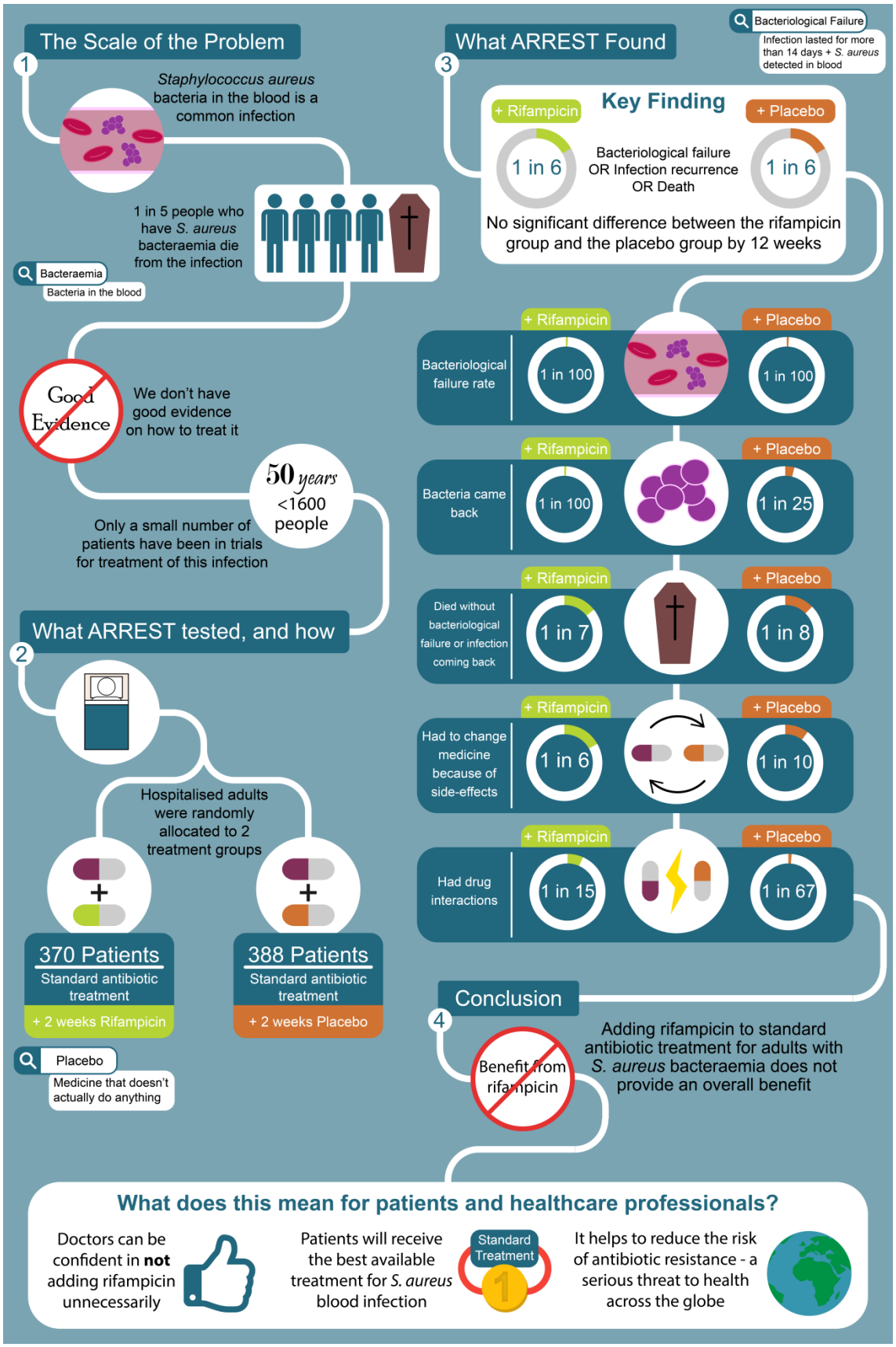


Figure 21 ARREST infographic

From Ms Bostock's perspective the trial has succeeded in involving patients and the public in a way that is rare in clinical trials of medicines. The team's support, patience and willingness to adapt and change the trial in response to public input have benefited both the public representative and also the trial. Being involved in the trial has enabled Ms Bostock to develop skills and understanding of clinical trials and PPI which she will use to benefit other research and it is hoped that researchers conducting similar trials will adopted some of the methods used in ARREST as a model of good PPI practice.

Summary and future research

In summary, the ARREST trial provides high quality data where there are almost none. The clinical management of infectious diseases and, in particular, the treatment of many common severe bacterial infections, lacks high quality clinical trial evidence. The situation is especially stark for *S. aureus* bacteraemia, probably the commonest, life-threatening, community and hospital-acquired infection worldwide. But whilst the ARREST trial addresses some of these inadequacies, it also leaves many questions unanswered as to how to improve outcomes from *S. aureus* bacteraemia.

The ARREST trial has exposed two possible windows in which to intervene. The first is in the acute phase, when *S. aureus* can be cultured from the bloodstream and a severe inflammatory response (or 'sepsis') can have rapidly fatal consequences. The interventions in this early phase are those targeted at more rapid recognition or diagnosis of *S. aureus* bacteraemia, and those which might enhance bacterial killing and control the detrimental effects of the inflammatory response. Future research therefore might investigate novel molecular techniques, perhaps based on rapid next-generation sequencing, to identify *S. aureus* from the blood and predict drug susceptibility such that effective antibiotic treatment can be given quickly. The question of whether intensified antibiotic therapy - be it different drugs, doses, or drug combinations - might speed bloodstream sterilisation very early in the infection and thereby improve outcomes has not been resolved by ARREST; although it has delineated the considerable challenges of conducting a trial to address this question. Likewise, early control of the inflammatory response, using corticosteroids or newer drugs targeted at specific molecules in the inflammatory cascade, might reduce early mortality and would be amenable to testing by clinical trials.

However, given the challenges we experienced conducting this trial, this is probably not the more important priority for future studies. Rather, the second interventional window in *S. aureus* bacteraemia is more easily accessible to trialists than the first window and, as our health economic analysis suggests, may also bring substantial cost savings. It opens after around 72-96 hours of active antibiotic treatment, once the acute phase is over, and concerns interventions to prevent, detect and manage the longer-term complications of the *S. aureus* bacteraemia, including disease recurrence. These complications include endocarditis, vertebral osteomyelitis, and other deep and potentially occult infection foci. As recent PET scan studies have shown,[71] perhaps the most promising strategies which should be prioritised for future research are those which aim to speed the detection of these complications and improve their antibiotic and surgical management; these could have major impacts on outcome and costs. A clinical trial investigating these strategies against current standards of care would be both feasible and likely to have a major impact upon clinical practice.

Chapter 7 Conclusions

Adjunctive rifampicin did not improve outcomes from *S. aureus* bacteraemia, with the exception of a modest reduction in disease recurrence which may be associated with reduced costs. Given the clinical effect had no impact on short-term or longer-term mortality, rifampicin significantly complicated other drug treatment, and widespread rifampicin use risks increasing resistance amongst *S. aureus* and other bacteria (for example, *Mycobacterium tuberculosis*), we consider that despite potential cost savings adjunctive rifampicin provides no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

Contribution of Authors

Professor Guy E Thwaites, Professor of Infectious Diseases, drafted the report
Dr Matthew Scarborough, Consultant in Infectious Diseases and Microbiology, helped draft the report
Alexander Szubert, Medical Statistician, performed the analysis
Marta Soares, Health Economist, designed the cost effectiveness analysis and drafted chapter 5
Pedro Saramago Goncalves, Health Economist, designed and implemented the cost effectiveness analysis and drafted chapter 5
Jennifer Bostock, Public and Patient representative, drafted PPI sections
Emmanuel Nsutebu, Consultant in Infectious Diseases, helped draft the report
Robert Tilley, Consultant Microbiologist, helped draft the report
Richard Cunningham, Consultant Microbiologist, helped draft the report
Julia Greig, Consultant in Infectious Diseases, helped draft the report
Sarah A Wyllie, Consultant Microbiologist, helped draft the report
Peter Wilson, Consultant Microbiologist, helped draft the report
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Gavin Barlow. Consultant infectious diseases, helped draft the report
N Claire Gordon, Infectious Diseases/microbiology trainee. Helped draft the report
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M Estee Török, Consultant in Infectious Diseases and Microbiology, helped draft the report
Martin J Llewelyn, Professor of Infectious Diseases, helped draft the report
Jonathan D Edgeworth, Consultant Microbiologist, helped draft the report
A Sarah Walker, Professor of Medical Statistics, analysed data and drafted the report

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Recruiting sites

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Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

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Title page

ARREST

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

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Abstract

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Background: *Staphylococcus aureus* bacteraemia is a common, frequently fatal infection. Adjunctive rifampicin may enhance early *S. aureus* killing, sterilise infected foci and blood faster, and thereby reduce the risk of dissemination, metastatic infection and death.

Objectives: To determine whether adjunctive rifampicin reduces bacteriological (microbiologically-confirmed) failure/recurrence or death through 12 weeks from randomisation. Secondary objectives included evaluating the impact of rifampicin on all-cause mortality, clinically defined failure/reccurrence or death, toxicity, resistance emergence, and duration of bacteraemia; and assessing rifampicin's cost-effectiveness.

Design: Parallel group, randomised (1:1), blinded, placebo-controlled multi-centre trial.

Setting: UK NHS Trust Hospitals.

Participants: Adult inpatients ($\geq$18 years) with methicillin resistant or susceptible *S. aureus* grown from $\geq$1 blood culture, who had received $\leq$96 hours of antibiotic therapy for the current infection, and without contraindications to rifampicin.

Interventions: Adjunctive rifampicin (600-900mg/day; oral or intravenous) or placebo for 14 days in addition to standard antibiotic therapy. Investigators and patients were blinded to trial treatment. Follow up was for 12 weeks (assessments at 3, 7, 10, and 14 days, weekly until discharge, final assessment 12 weeks post-randomisation).

Main outcome measures: The primary outcome was all-cause bacteriological (microbiologically-confirmed) failure/recurrence or death through 12 weeks from randomisation.

Results: Between December 2012 and October 2016, 758 eligible participants from 29 United Kingdom hospitals were randomised: 370 to rifampicin and 388 to placebo. The median (interquartile range) age was 65(50-76) years. 485(64.0%) infections were community-acquired and 132(17.4%) nosocomial; 47(6.2%) were caused by methicillin-resistant *S. aureus*. 301(39.7%) had an initial deep infection focus. Standard antibiotics were given for median(IQR) 29(18-45) days; 619(81.7%) received flucloxacillin. By 12-weeks, 62/370 (16.8%) rifampicin versus 71/388 (18.3%) placebo participants experienced bacteriological (microbiologically-confirmed) failure/recurrence or died (absolute risk difference=-1.4% (95% confidence interval -7.0%-4.3%); hazard-ratio=0.96 (0.68-1.35) p=0.81). Comparing rifampicin with placebo there were 4(1.1%) versus 5(1.3%)

bacteriological failures (p=0.82), 3(0.8%) versus 16(4.1%) bacteriological recurrences (p=0.01), and 55(14.9%) versus 50(12.9%) deaths without bacteriological failure/recurrence respectively (p=0.30). Over 12-weeks, there was no evidence of differences in clinically-defined failure/recurrence/death (p=0.84), all-cause mortality (p=0.60), serious (p=0.17) or grade-3/4 (p=0.36) adverse events. However, 63(17.0%) rifampicin versus 39(10.1%) placebo experienced antibiotic or trial-drug-modifying adverse events (p=0.004) and 24(6.5%) versus 6(1.5%) respectively experienced drug-interactions (p=0.0005). Evaluation of the costs and Health Related Quality of Life impacts revealed that an episode of *S. aureus* bacteraemia costs £12 197 on average over 12 weeks. Rifampicin was estimated to save 10% of episode costs (P=0.14). After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (SE=0.004 QALY).

Limitations: Reflecting clinical practice, participants were heterogeneous in disease severity, limiting ability to investigate some clinically relevant subgroups. A minority initiated open-label rifampicin or stopped blinded trial drug early, predominantly for drug-drug interactions or adverse events.

Conclusions: Adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

Future work: Given the substantial mortality, other antibiotic combinations or improved source management should be investigated.

Study registrations: Current Controlled Trials ISRCTN37666216; EUDRACT 2012-000344-10; and CTA: 00316/0243/001

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List of abbreviations

AE	**Adverse event**
AIC	**Akaike Information Criteria**
ALT	**Alanine transaminase**
ALP	**Alkaline phosphatase**
AST	**Aspartate aminotransferase**
BD	**Twice daily**
BNF	**British National Formulary**
CI	**Confidence interval**
CRF	**Case Report Form**
CRP	**C-reactive protein**
CT	**Computed tomography**
CTA	**Clinical Trials Authorisation**
CTC	**Common Toxicity Criteria**
CTU	**Clinical Trials Unit**
DMC	**Data Monitoring Committee**
DNA	**Deoxyribonucleic acid**
eCRF	**Electronic Case Report Form**
EDTA	**Ethylenediaminetetraacetic acid**
EQ-5D	**European Quality of Life 5 Dimensions (questionnaire)**
ERC	**Endpoint Review Committee**
EudraCT	**European Union Drug Regulatory Agency Clinical Trial**
EVPI	**Expected value of perfect information**
GCP	**Good Clinical Practice**
GLM	**Generalised Linear Model**
HDU	**High dependency unit**
HIV	**Human Immunodeficiency Virus**
HR	**Hazard ratio**
HRQoL	**Health Related Quality of Life**
ICH	**International Conference on Harmonisation of Technical Requirements for**

	Registration of Pharmaceuticals for Human Use
IMP	**Investigational medicinal product**
INB	**Incremental net benefit**
INHB	**Incremental net health benefit**
IQR	**Interquartile range**
ISRCTN	**International Standard Randomised Controlled Trial Number**
ITU	**Intensive care unit**
IV	**Intravenous**
LR	**Legal representative**
MedDRA	**Medical Dictionary for Regulatory Activities**
MRC CTU at UCL	**Medical Research Council Clinical Trials Unit at University College London**
MRI	**Magnetic resonance imaging**
MRSA	**Methicillin-resistant *Staphylococcus aureus***
MSSA	**Methicillin-sensitive *Staphylococcus aureus***
NHB	**Net health benefit**
NHS	**National Health Service**
NICE	**National Institute for Health and Care Excellence**
NNT	**Number needed to treat**
OD	**Once daily**
PD	**Pharmacodynamic**
PET	**Positron emission tomography [scan]**
PI	**Principal Investigator**
PK	**Pharmacokinetics**
PPI	**Patient and public involvement**
QALY	**Quality adjusted life year**
RD	**(Absolute) risk difference**
RNA	**Ribonucleic acid**
SAE	**Serious adverse event**
SAB	***Staphyloccocus aureus* bacteraemia**

SE	**Standard Error**
SPC	**Summary of Product Characteristics**
SUSAR	**Suspected unexpected serious adverse reaction**
TOE	**Transoesophageal echocardiography**
UCL	**University College London**
ULN	**Upper limit of normal**
UKCIRG	**United Kingdom Clinical Infection Research Group**

Plain English Summary

Staphylococcus aureus (or *S. aureus*) is a germ which can cause serious infections, particularly when it gets into the bloodstream. Doctors use an antibiotic to cure *S. aureus* but sometimes the antibiotic does not succeed in curing the infection and sometimes the infection comes back.

The ARREST trial tested whether or not giving two weeks of an extra antibiotic, called rifampicin, in addition to the standard antibiotic, would help sick people with *S. aureus* blood infections. The aim was to find out if rifampicin could cure more people, possibly faster, to see whether it caused more or less side-effects and to see if the germ that causes the infection became resistant to rifampicin.

In total, 770 patients from the United Kingdom (UK) aged 18 to 100 years participated. The participants all received the same standard antibiotic that they would have received if they had not joined the study. In addition 370 patients received two weeks of rifampicin and 388 patients received two weeks of placebo (dummy).

The ARREST study found that people who had rifampicin in addition to standard antibiotic treatment did no better overall than people who had just standard antibiotic treatment, in terms of how successful their treatment was. People in the group who had rifampicin were no more likely to have serious or severe side-effects than those in the group who had placebo. There was some evidence that rifampicin reduced the risk of the infection coming back again. But this did not reduce the overall deaths. *S. aureus* from only two people's blood developed resistance to rifampicin.

The results suggest that people with *S. aureus* blood infections are unlikely to benefit from adding rifampicin to standard antibiotic treatment. The study included a wide range of patients with *S. aureus* blood infections, so the results apply widely.

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Scientific Summary

Background

Staphylococcus aureus bacteraemia is a common and serious infection, with an associated mortality of approximately 25%. Once *S. aureus* enters the blood stream it can disseminate to infect almost any organ of the body, but most commonly affects the bones, joints and heart valves. Despite the infection's severity, the evidence guiding optimal antibiotic therapy is weak as fewer than 1500 patients have been included in 16 randomised controlled trials investigating *S. aureus* bacteraemia treatment. Therefore which antibiotics are most effective, their route of administration and duration, and whether antibiotic combinations are better than single agents is unknown. We hypothesised that adjunctive rifampicin would reduce bacteriologically-confirmed failure/recurrence or death, by enhancing early *S. aureus* killing, sterilising infected foci/blood faster, and reducing risks of dissemination and metastatic infection.

Objectives

The primary objective of the trial was to investigate the impact of adjunctive rifampicin on bacteriologically confirmed failure/recurrence or death through 12 weeks from randomisation. Secondary objectives included evaluating the impact of rifampicin on all cause mortality up to 14 days from randomisation, on clinically-defined failure/recurrence or death, toxicity (serious or grade 3 or 4 adverse events (AEs) or modification of any treatment due to drug interactions), emergence of resistance, and duration of bacteraemia; and assessing the cost-effectiveness of adjunctive rifampicin for *S. aureus* bacteraemia in the NHS.

Methods

Design:

Parallel group, randomised (1:1), blinded, placebo controlled multi-centre trial.

Setting:

29 large acute NHS Trusts. Patients were identified through the clinical microbiology laboratory and the infectious diseases/microbiology consult service at each centre.

Participants:

Inclusion Criteria:

- Adult inpatients (18 years or older)
- *Staphylococcus aureus* (methicillin-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) provided written informed consent

Exclusion criteria:

- Infection not caused by *S. aureus* alone in the opinion of the infection specialist (e.g. *S. aureus* 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*
- 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

Incapacitated adults were eligible provided they had an appropriate legal representative to provide consent.

Interventions:

Eligible patients were randomised to standard intravenous antibiotic therapy of the attending physician's choice plus either 14 days of placebo or rifampicin (900mg/24 hours if ≥60kg; 600mg/24 hours if<60kg). Rifampicin could be administered via intravenous (IV) or oral route according to patient status and either once daily (OD) or twice daily (BD).

Follow up:

All participants were followed up on days 3, 7, 10, 14, weekly until discharge, and the final assessment took place at 12 weeks post randomisation.

Sample size:

770 patients were recruited, providing 80% power 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, assuming 10% loss to follow-up by 12 weeks (two-sided alpha=0.05).

Health economics:

Cost and health outcomes for patients with *S. aureus* bacteraemia were evaluated using data from the ARREST trial. Costs considered were those incurred by the NHS and encompassed

antibiotic therapy, admissions to secondary care (including investigations and procedures undertaken while hospitalised) and consultations with healthcare providers after hospital discharge from first admission. Health outcomes were measured as quality-adjusted life years (QALYs), calculated from EQ-5D-3L responses collected in the trial and imputed to account for missingness. Costs and QALYs were measured only for 84 days (i.e. 12 weeks), the maximum duration of active follow-up. The analyses used a regression approach to explore determinants of costs and QALYs on baseline covariates, including treatment group, which allowed for a cost-effectiveness analysis to be conducted. Decision uncertainty was accounted for through probabilistic modelling.

Results

Baseline characteristics:

Between December 2012 and October 2016, 758 eligible participants from 29 United Kingdom hospitals were randomised: 370 to rifampicin and 388 to placebo. 495 (65.3%) were men. The median (interquartile range (IQR)) age was 65 (50-76) years, and Charlson co-morbidity score was 2 (0-3). 70 (9.2%) participants were in an intensive care unit. Mean (Standard Error) CRP was 164 (3.7) mg/L. 127 (16.8%) had consent provided by a legal representative due to incapacity. 485 (64.0%) infections were community-acquired, with only 132 (17.4%) nosocomial. 47 (6.2%) infections were caused by methicillin-resistant *S. aureus* (MRSA). No patients were known to have rifampicin-resistant *S. aureus* bacteraemia at randomisation. The initial focus was deep in 301 (39.7%) (including 33 (4.4%) with endocarditis and 14 (1.8%) with infected prostheses); 130 (17.2%) were due to infected central/peripheral lines; 138 (18.2%) associated with skin/soft tissue infections; another type of focus was identified in 49 (6.5%) and not established in 139 (18.3%). At randomisation, participants had received median (IQR) 62 (42-75) hours of active antibiotics.

Follow up:

22 (2.9%) participants withdrew consent. At the 12-week visit only 39 (5.1%) had unknown vital status and 65 (8.6%) were not assessed for signs/symptoms of *S. aureus* infection (including consent withdrawals).

744 (98.2%) participants initiated blinded trial drug (96 (12.7%) intravenously, 595 (78.5%) 900mg daily), a median (IQR) 68 (48-85) hours after starting active antibiotics for the current infection. Trial drug was continued for median (IQR) 12.6 (6.0-13.2) days in rifampicin participants versus 13.0 (11.3-13.5) days in placebo participants ($p<0.0001$; primarily due to antibiotic-modifying AEs and drug-drug interactions, see below). Percentages reporting

missing any doses ranged from 9.5%-16.2% but did not differ between randomised groups (global p=0.72).

A substantial variety of 'backbone' active antibiotics were used, although flucloxacillin was given in 619 (81.7%), and vancomycin or teicoplanin in 380 (50.1%) at some point in the primary treatment course. The numbers of antibiotics used (median (IQR) 3 (2-4)) and the duration of anti-staphylococcal treatment (median (IQR) 29 (18-45) days) was similar between groups. 32 (8.6%) rifampicin participants versus 52 (13.4%) placebo participants used open-label rifampicin (p=0.04), initiated median (IQR) 14 (7-18) days after randomisation. 159 placebo versus 142 rifampicin participants had a deep focus which was drained/removed in 35 (22.0%) versus 29 (20.4%), a median (IQR) 5 (2-12) and 3 (1-6) days from randomisation respectively.

Primary endpoint:

By 12-weeks, 62/370 (16.8%) rifampicin versus 71/388 (18.3%) placebo participants experienced bacteriological failure/recurrence or died (absolute risk difference (RD)=-1.4% (95% confidence interval -7.0%,+4.3%); hazard-ratio(HR)=0.96 (0.68-1.35) p=0.81). Comparing rifampicin with placebo there were 4(1.1%) versus 5(1.3%) bacteriological failures (p=0.82), 3(0.8%) versus 16(4.1%) bacteriological recurrences (p=0.01), and 55(14.9%) versus 50(12.9%) deaths without bacteriological failure/recurrence respectively (p=0.30).

Secondary endpoints:

Clinically-defined failure/recurrence or death occurred in 76 (20.5%) rifampicin versus 86 (22.2%) placebo participants (RD=-1.4% (95% CI -7.4%,+4.7%); HR=0.97 (0.71-1.32) p=0.84). Comparing rifampicin and placebo there were 23 (6.2%) versus 25 (6.4%) failures (p=0.97), 8 (2.2%) versus 23 (5.9%) recurrences (p=0.01), and 45 (12.2%) versus 38 (9.8%) deaths without clinically-defined failure/recurrence respectively (competing-risks p=0.22). By 12-weeks, 56 (15.1%) rifampicin versus 56 (14.4%) placebo participants died (RD=+1.0% (95% CI -4.3%,+6.2%); HR=1.10 (0.76-1.60) p=0.60). 25 (6.8%) rifampicin versus 17 (4.4%) placebo participants died before 2 weeks (HR=1.60 (0.86-2.95) p=0.13). 14 rifampicin versus 16 placebo deaths were adjudicated definitely *S. aureus*-related, 14 versus 12 probably *S. aureus*-related, and 8 versus 4 possibly *S. aureus*-related, respectively. 18 versus 23 were not attributed to *S. aureus* (remainder unattributable) (overall p=0.64). There was no difference in longer-term (post-week 12) survival between the groups (p=0.69). There was no evidence that duration of bacteraemia was significantly shorter in those randomised to rifampicin (global p=0.66). Two (0.5%) rifampicin participants developed new rifampicin-resistant *S. aureus*

bacteraemia 7 and 42 days after randomisation (p=0.24). One occurred on day 7 (followed by rifampicin discontinuation on day 11 and bacteriological failure on day 14); the other on day 42 (prescribed 14 days rifampicin; bacteriological recurrence on day 42).

Safety:

By 12-weeks, 101 (27.3%) rifampicin versus 94 (24.2%) placebo participants experienced 112 versus 116 serious adverse events (HR=1.21 (95% CI 0.92-1.61) p=0.17). Two rifampicin participants with pre-existing liver disease experienced non-fatal hepatic failure. 129 (34.9%) rifampicin versus 131 (33.8%) placebo participants experienced 209 versus 193 grade 3/4 AEs (HR=1.12 (95% CI 0.88-1.43) p=0.36). Most notable was a trend towards more renal grade 3/4 AEs with rifampicin which occurred in 19 (5.1%) versus 9 (2.3%) placebo participants (p=0.053); 17 versus 6 respectively being acute kidney injury. 63 (17.0%) rifampicin versus 39 (10.1%) placebo experienced 89 versus 52 antibiotic-modifying AEs (sub-distribution HR=1.78 (1.20-2.65) p=0.004). Gastrointestinal disorders (24 versus 8 participants, respectively, p=0.003) and renal/urinary disorders (8 versus 1 participants, respectively, p=0.02) were more common with rifampicin. 24 (6.5%) rifampicin versus 6 (1.5%) placebo experienced drug-interactions (p=0.0005); 13 versus 4 led to discontinuation of trial drug (p=0.03), 14 versus 3 respectively led to grade 1/2 AEs (p=0.006), and 5 versus 2 respectively to grade 3/4 AEs (p=0.27).

Health economics:

We found that an episode of *S. aureus* bacteraemia costs, on average, £12 197 over 12 weeks. The cost categories that contributed the most to costs were length of stay (primary hospital admission and readmissions) and procedures undertaken in hospital. Baseline determinants of higher episode costs were nosocomial *S. aureus* bacteraemia (costs 41% higher); a deep primary focus of infection (costs 43% higher); endocarditis (costs 65% higher), high neutrophil count (>9x10^9/L, costs 33% higher), and if the patient was comatose (costs 32% higher). Age, gender, BMI, Charlson index and methicillin resistance did not affect costs.

Analysis indicates that adjunctive rifampicin may save 10% of episode costs, with larger savings happening after 14 days. Despite not being statistically significant, this result is consistent with the small reduction in recurrences that probably drives shorter hospital stays. It is however, important to note that the costs of rifampicin toxicity and drug-drug interactions were not included in this analysis.

As expected in this population of acutely ill patients, very low values of the EQ5D score were observed at baseline (mean EQ-5D score of 0.10). Determinants of QALYs in the sample were baseline EQ5D score (0.0064 QALYs lost for every 0.1 decrease in baseline EQ-5D);

higher age (up to 0.044 QALY loss); Charlson index (up to 0.024 QALY loss) and coma (mean QALY loss of 0.020). After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (SE=0.004 QALY).

Conclusions

Adjunctive rifampicin does not reduce mortality from *S. aureus* bacteraemia. It may reduce the risk of disease recurrence. Our trial suggests this effect had no impact on short-term or longer-term mortality, but it may reduce costs. However, rifampicin significantly complicates other drug treatment. We therefore consider that adjunctive rifampicin provides no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

Trial registrations

Current Controlled Trials ISRCTN37666216; EUDRACT 2012-000344-10; and CTA: 00316/0243/001

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Chapter 1 Introduction

(Note: this chapter includes material that has been adapted from the trial protocol which has been published in Trials 2012 13:241)

Background

Staphylococcus aureus bacteraemia is one of the most common and serious bacterial infections worldwide. There were over 12,000 cases of *S. aureus* bacteraemia in the UK in 2016/2017, and around 25% of these patients die.[1,2] 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 methicillin-resistant. Combination antimicrobial therapy is generally not recommended, except in severe methicillin-resistant *S. aureus* (MRSA) infections (e.g. endocarditis) or in the presence of prosthetic joint infections.[3-6] Most of the recommendations are based on uncontrolled observational studies and clinical experience, and views of how to manage *S. aureus* bacteraemia differ widely.[7,8]

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, it has been 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.

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 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 Human Immunodeficiency Virus (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.

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.[29,30] 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; subgroup 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 one 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 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] A recent observational study of 964 patients with *S. aureus* bacteraemia reported 512 (53%) of them received combination therapy and the majority (301/512, 59%) received rifampicin.[33] Combination therapy was not associated with reduced mortality in all patients, but was associated with reduced deaths and infection-related complications in those suffering from device-related infections.

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).[34] Rifampicin was used to treat 21% of MRSA bacteraemia and 15% of methicillin-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).

Rationale

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 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).[4,6] But with weak support for these recommendations it is unsurprising few physicians follow them in practice. The ARREST trial was designed to provide a definitive answer to the role of adjuvant rifampicin therapy in the treatment of *S. aureus.*

Objectives

The hypothesis addressed by the ARREST trial 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 was to investigate the impact of adjunctive rifampicin on bacteriologically-confirmed failure/recurrence or death through 12 weeks from randomisation. Secondary objectives included evaluating the impact of rifampicin on all cause mortality up to 14 days from randomisation, on clinically-defined failure/recurrence or death, toxicity (serious and grade 3/4 adverse events (AEs), any modification of treatment due to drug interactions), emergence of resistance and duration of bacteraemia; and assessing the cost-effectiveness of adjunctive rifampicin for *S. aureus* bacteraemia in the NHS.

Substudies

There were three ancillary studies to the main trial. First, with assistance from the trial's public and patient representative, Jennifer Bostock, we examined the process of obtaining consent to enter the trial. Patients/legal representatives who did not consent to participation in the trial were offered the opportunity to complete a questionnaire exploring reasons for this; participants/legal representatives at one trial centre who did consent were offered the opportunity to be interviewed by the ARREST patient and public representative to explore their experiences of trial participation.

Samples were collected for two further ancillary studies for which funding will be sought seperately. Participants enrolled at Guy's & St Thomas' NHS Foundation Trust, Cambridge University Hospitals NHS Trust, Oxford Univerity Hospitals NHS Trust, The Royal Liverpool and Broadgreen University Hospitals NHS Trust and Brighton and Sussex University Hospitals NHS Trust were approached for additional consent for a pharmacokinetic/pharmacodynamic (PK/PD) substudy – a population PK/PD study of rifampicin, flucloxacillin and vancomycin for the treatment of *S. aureus*. The aim of the 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.

All participants were also approached for additional consent for the host DNA/RNA substudy to investigate the influence of host and bacterial genetics on disease severity and outcome from *S. aureus*. The 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 samples for the PK/PD and DNA/RNA substudies have been archived at the King's College London Biobank until funding has been secured.

Chapter 2 Methods

(Note: this chapter includes material that has been adapted from the trial protocol which has been published in Trials 2012 13:241.)

Trial setting

Patients were recruited from 29 large UK NHS Hospital Trusts: Guy's and St Thomas' NHS Foundation Trust; Oxford University Hospitals NHS Trust; University College London Hospitals NHS Foundation Trust; Royal Free London NHS Foundation Trust; King's College Hospital NHS Foundation Trust; Brighton and Sussex University Hospitals NHS Trust; The Royal Liverpool and Broadgreen University Hospitals NHS Trust; Sheffield Teaching Hospitals NHS Foundation Trust; Cambridge University Hospitals NHS Foundation Trust; Royal United Hospital Bath NHS Trust; Royal Devon and Exeter NHS Foundation Trust; Plymouth Hospitals NHS Trust; Hull and East Yorkshire Hospitals NHS Trust; South Tees Hospitals NHS Foundation Trust; Heart of England NHS Foundation Trust; St George's Healthcare NHS Trust; Portsmouth Hospitals NHS Trust; University Hospital Southampton NHS Foundation Trust; Blackpool Teaching Hospitals NHS Foundation Trust; The Leeds Teaching Hospital NHS Trust; Aintree University Hospital NHS Foundation Trust; Bradford Teaching Hospitals NHS Foundation Trust; County Durham and Darlington NHS Foundation Trust; Dartford & Gravesham NHS Trust; North Cumbria University Hospitals; University Hospitals of Leicester NHS Trust; Wirral University Teaching Hospital NHS Foundation Trust; The Newcastle upon Tyne Hospitals NHS Foundation Trust; and Salford Royal NHS Foundation Trust.

The main criteria for selecting participating hospitals was that they had an existing *S. aureus* bacteraemia ward consultation service, sufficient numbers of *S. aureus* bacteraemias to be able to recruit patients (potential to recruit a minimum of one patient per month), as well as the necessary research infrastructure to conduct the trial.

The overall trial design is summarised in **Figure 1**.

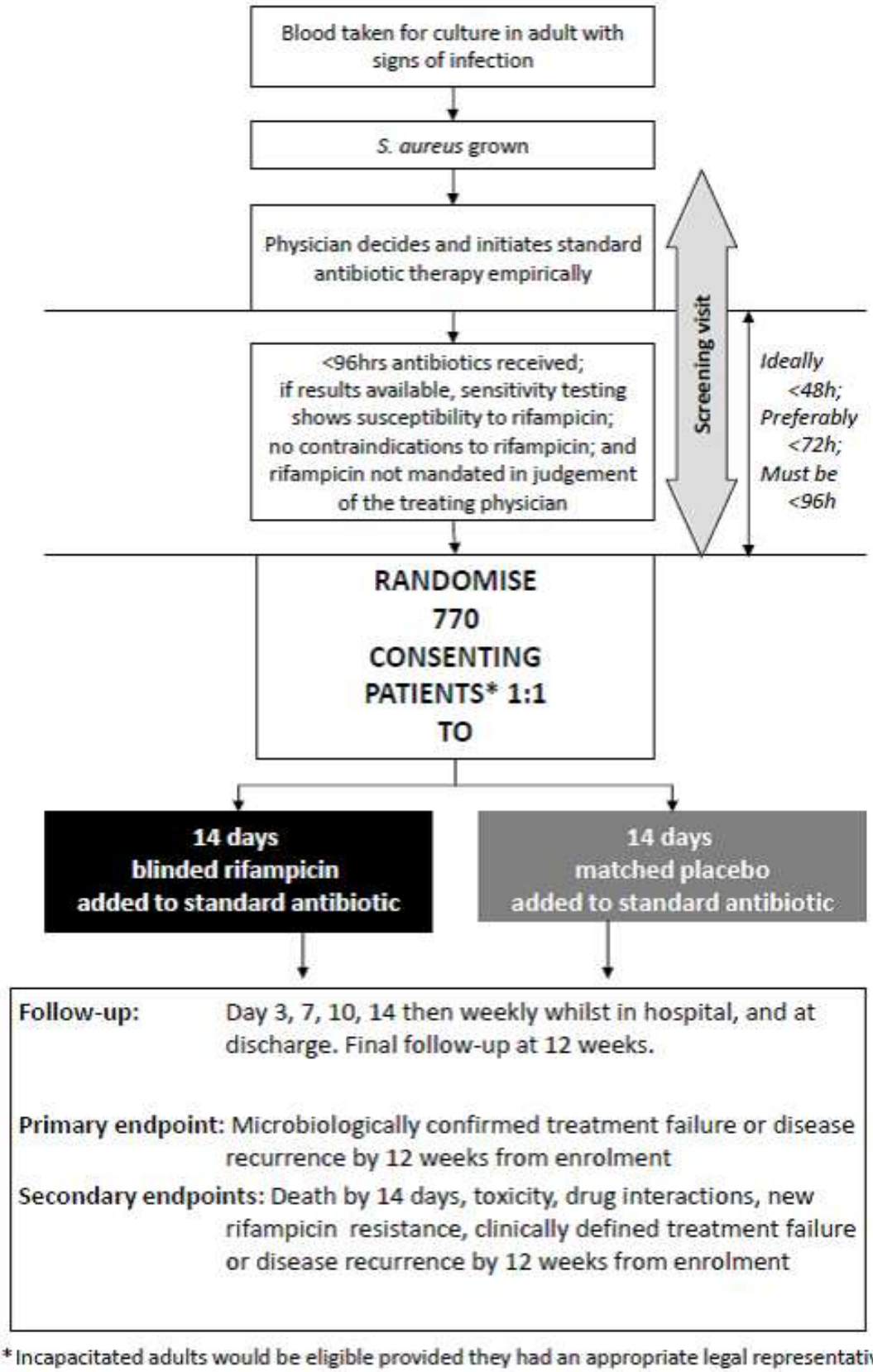


Figure 1: Trial Schema

Patient selection

As *S. aureus* bacteraemia is a serious infection whose standard treatment requires IV antibiotics, all eligible patients were hospital inpatients at the time of recruitment. Patients were identified via the clinical microbiology laboratory and the infectious diseases/microbiology consult service at each centre. When possible, patients were screened for eligibility on the day that their blood cultures flagged positive with *S. aureus*. Written informed consent was obtained from patients. Incapacitated adults were eligible provided they had an appropriate legal representative (LR) to provide consent. The Principal Investigator (PI) or another experienced independent physician was required to 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 was confirmed, then written informed consent was 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).

INCLUSION CRITERIA

The trial enrolled adults aged 18 years or older who had *S. aureus* (methicillin-susceptible or resistant) grown from at least one blood culture, had received less than 96 hours of active antibiotic therapy for the current infection (not including rifampicin, and excluding any stat doses), and the patient or LR had provided written informed consent for participation in the trial.

Although the formal inclusion criteria stated that patients must have received <96 hours of active antibiotic therapy for the current infection, 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] Therefore, patients were included in the trial as soon after initiation of active antibiotic therapy as possible, within 48 hours wherever possible and ideally within 72 hours.

EXCLUSION CRITERIA

Patients were excluded from the trial if they had infection not caused by *S. aureus* alone in the opinion of the infection specialist (e.g. *S. aureus* was considered a blood culture contaminant, or polymicrobial culture with another organism likely to be contributing clinically to the current infection); if sensitivity results were already available and demonstrated rifampicin resistant *S. aureus* (defined by British Society for Antimicrobial Chemotherapy *in vitro* disc susceptibility testing or by Vitek testing); if the infection specialist, in consultation with the treating physician, considered rifampicin to be contraindicated for any reason; if the infection specialist, in consultation with the treating physician, considered rifampicin treatment to be mandatory for any reason; if the infection specialist suspected active infection with *Mycobacterium tuberculosis;* or if the patient had been previously been randomised in ARREST for a prior episode of *S. aureus* bacteraemia.

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

Randomisation

Eligibility was confirmed by ARREST site investigators (PI, co-principal investigator, or research nurse) via the online ARREST database, and patients were randomised into two parallel groups in a 1:1 ratio, to standard intravenous antibiotic therapy plus 14 days placebo, or standard intravenous antibiotic therapy plus 14 days rifampicin. The choice and duration of the standard antibiotic therapy was left to the attending physician. Randomisation was stratified by clinical centre, as blinded drug (in fully made-up and labelled treatment packs) was pre-shipped to local pharmacies. A computer-generated sequential randomisation list using variably-sized permuted blocks was prepared by the trial statistician and incorporated securely into the online trial database. The list was concealed until allocation, after eligibility was

confirmed by researchers at the local hospitals, who then performed the randomisation. A 24 hour web-based randomisation service was provided via the online ARREST database.

Trial Intervention

Rifampicin/placebo was given by oral or intravenous route, according to the attending physician's preference and the patient's status. Provided a patient could swallow safely, the preference was to use rifampicin orally. Intravenous administration was permitted for patients that were not able to swallow or absorb tablets. Rifampicin is a well-established, widely used drug, and was not used outside its licensed indication during the course of the trial.

The oral Investigational Medicinal Product (IMP) was prepared by a Clinical Trials Supplier (Sharp Clinical Services). It was supplied as rifampicin 300 mg capsules (Sanofi-Aventis, UK) Summary of Product Characterisitics (SPC): http://www.medicines.org.uk/emc/medicine/21223/SPC/Rifadin+300mg+Capsules/, or placebo oral 300mg capsules containing cellulose. The placebo capsules were over-encapsulated so that they were identical in appearance to the rifampicin capsules. The capsules were supplied to trial centres as individual participant blinded treatment packs so they were dosed and dispensed in the same way.

The IV IMP was provided via standard hospital stock and consisted of either rifampicin for intravenous infusion (Rifampicin 600 mg for intravenous injection (Sanofi-Aventis, UK) SPC http://www.medicines.org.uk/emc/medicine/6435), or standard saline as the placebo. Participants receiving intravenous infusions in the intensive care unit could have their infusion volume altered in accordance with standard local practice and the SPC. The trial pharmacist at each hospital had access to a copy of the randomised allocations for each ARREST trial number for their centre in order to prescribe IV rifampicin if required.

DOSE

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

- those <60kg received 600mg every 24 hours
- those ≥60kg received 900mg every 24 hours

Oral doses could be given once or twice daily, according to clinician and patient preference, and subgroup analysis according to initial oral dosing frequency (elicited at randomisation) was pre-specified. If taken twice daily, 900mg daily (3 capsules) was taken as unequal divided doses (600mg am, 300mg pm): as rifampicin can also be taken once daily, this provided adequate exposure.

Where IV was prescribed, it was administered to the patient over 2-3 hours.

BLINDING AND MASKING

Rifampicin for intravenous infusion is supplied as a vial of red powder that requires reconstitution with 10 ml of water for infusion with saline. The resulting fluid for intravenous infusion is orange. It was impossible to safely and reliably produce a red-powder placebo which produced an identical orange infusion. Therefore, the ward nurse making up the intravenous drug for the infusion was not blind to the treatment, nor was the hospital pharmacist dispensing either rifampicin or saline for IV administration. The ward nurses were instructed not to divulge the colour of the drug to the physicians caring for the patient. In addition, the infusion was covered by an opaque bag to disguise the treatment. As far as possible the trial physicians, research nurses, and other physicians caring for the patient remained blinded, as were all trial and data management staff except for statisticians.

Rifampicin can turn urine (and tears/sweat) reddish-orange. It is impossible to safely replicate this effect with a placebo; therefore urine discolouration was a potential source of unblinding, particularly of the participant. There is, however, considerable inter- and intra-individual variability in rifampicin's effect on urine colour. In addition, the opportunity for physicians to examine the urine at the bedside only occurred in participants with urinary catheters. Catheters were not required by all participants and were removed at the earliest opportunity. We also limited the opportunity for physicians to inspect urine by ensuring the catheter bags were emptied regularly and urine was not allowed to accumulate in large volumes. The success of blinding was assessed at the final 12 week visit, when physicians and participants were asked which treatment they believed they had received.

DOSE MODIFICATIONS, INTERRUPTIONS AND DISCONTINUATIONS

Toxicity was managed in both randomised groups according to standard clinical practice. In some situations, changes in the patient's condition meant that the dose of rifampicin needed to be reduced or stopped altogether. Wherever possible, this was done without unblinding. Unblinding was only performed when knowledge of the allocated treatment had a direct bearing on clinical management. Patients were not put at any additional risk by trial randomisation, as any patient that developed a suspected adverse drug reaction to study drug was managed as if they were receiving rifampicin, and study drug was discontinued.

The most important rifampicin toxicity is liver impairment, although serious hepatic toxicity is rare (<1% of patients). The study drug (rifampicin/placebo) was withdrawn without unblinding if significant liver toxicity was observed (blood Aspartate aminotransaminase (AST)/Alanine transaminase (ALT) >5x upper limit of normal (ULN)) without other probable causes, and was withdrawn for grade 4 liver toxicity (blood AST/ALT > 10xULN) regardless of probable cause. The dose of study drug was reduced if less severe liver dysfunction occured according to the judgement of the treating physician. Other medications (including other antibiotics) were 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 was not mandated for patient management.

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).

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

- where other antibiotics being used to treat *S. aureus* bacteraemia were 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 became available after the patient had been randomised and initiated rifampicin/placebo and indicated resistance to rifampicin. This was to prevent any toxicity from an additional but ineffective drug

being used. Primary rifampicin resistance was expected in <1% enrolled patients based on observational study data.[34]

OTHER ANTIBIOTICS

Infection specialist consultation, with advice on management to non-specialists caring for the trial participants, followed normal clinical practice in all sites. Attending physicians could change 'backbone' antibiotics according to clinical need and infection specialist advice and use open-label rifampicin after 14 days; where judged clinically necessary they could stop blinded trial drug before 14 days to use open-label rifampicin, with participants continuing follow-up "off study drug, on study".

Assessments and follow-up

TRIAL ASSESSMENT SCHEDULE

All participants were followed by the centre trial teams for 12 weeks for evaluation of all-cause mortality, morbidity and toxicity. To assess the outcome measures, patients were visited on the ward by the centre PI, one of their clinical team (e.g. Specialist Registrar), or a research nurse. The schedule for timing, frequency and method of collection of all study data is summarised below. Assessments were performed as close as possible to the required time point.

SCREENING AND RANDOMISATION VISITS

Patients were identified through the clinical microbiology laboratory and the infectious diseases/microbiology consult service of each centre. All the trial centres ran a clinical consult service for all cases of *S. aureus* bacteraemia and identified such patients as soon as their blood cultures become positive. The screening visit took place as soon as possible after a potential patient had 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 was essential that patients were 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 patient consent to recruitment was requested within two hours of the screening assessment wherever possible, and ideally within four hours.

Written informed consent to enter into the trial and be randomised was obtained from patients or a person with responsibility (including legal authorities) (a legal representative, LR).

After consent was obtained from the patient or their legal representative, clinical information including medical history and examination, and weight were recorded. C-reactive protein (CRP) and liver function tests are routine investigations for patients with suspected *S. aureus* bacteraemia and were also recorded

Randomisation took place as soon as possible after eligibility was confirmed and consent was signed.

FOLLOW UP

At each main clinical assessment (days 0, 3, 7, 10, 14, weekly until discharge, week 12 final visit), the following was 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
- 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 were recorded. With the exception of events leading to modification/interruption/discontinuation of the study drug, the severity and likely relationship of these adverse events to rifampicin/placebo was documented by a physician. Any drug interactions leading to dose modification of any drug (including concomitant medications) were also be recorded.
- Assessment of adherence to rifampicin/placebo (missed pills)
- Assessment of resource utilisation (medications, procedures, laboratory tests and other relevant resource use categories)

Blood cultures were 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 could be taken at any other timepoints necessary for clinical management: but were additionally taken if potential treatment failure is suspected (e.g. in patients who still had a positive blood culture on day 7 and in whom transoesophageal echocardiography (TOE) was being considered) or where *S. aureus* bacteraemia recurrence was suspected. C-reactive protein was measured on days 0, 3, 10 and 14 to assess treatment response. ALT, bilrubin, alkaline phosphatase was assessed on days 3 and 10 to evaluate liver toxicity. Full blood count was 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) were taken from patients on day 0 stored for later DNA/RNA extraction where consent had been provided for this. If a patient had already been discharged from hospital before day 7, 10, or 14, these additional investigations requiring a blood draw (culture, CRP, ALT (Alkaline phosphatase), ALP, bilirubin, serum storage) were not required so patients were not asked to attend ARREST specific outpatient appointments on these days, but returned at 12 weeks only.

EQ-5D for quality of life assesment was administered on days 0, 7, 14 and at the final visit.

Those patients discharged before 12 weeks were managed and followed-up through each centre's infectious diseases outpatient clinic. Final follow-up at 12 weeks was either by a ward visit (if the patient was still admitted to hospital) or by a clinic visit with interview and clinical assessment. In the event that the patient was unable to attend clinic, the follow-up visit could take place over the phone. If failure or *S. aureus* bacteraemia recurrence was suspected then repeat blood cultures were performed together with a clinical assessment and EQ-5D.

The trial end was defined as the final 12 week visit of the last patient to be randomised. At the end of the trial, vital status of all participants was ascertained from electronic NHS records, and consent was sought for this.

Procedures for assessing efficacy

The trial's primary outcome was:

- Time to death or bacteriologically confirmed failure or disease recurrence up to 12 weeks from randomisation

This outcome measure was 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 or telephone call). Consent to contact the patient's GP was also obtained.

The definition of bacteriologically confirmed failure was:

(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 bacteriologically confirmed disease recurrence was :

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

As defined, failure reflected both the speed of killing of *S. aureus* and sterilisation of infected foci/blood, and both failure and recurrence reflected the risk of dissemination and metastatic infection. Outcome measures included *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 was not considered failure. Additional blood cultures were requested as soon as the PI/study physician suspected failure or recurrence. All bacterial isolates (initial and all subsequent) from patients randomised in the trial were originally intended to be genotyped by multi-locus sequence and spa-typing and tested for susceptibility to rifampicin.

A substantial proportion of bacteriological failure/recurrences did not have both baseline and failure/recurrence isolates stored (17 (61%) of 28 failures/recurrences where *S. aureus* was isolated from a sterile site). In order to avoid excluding a substantial proportion of potential primary endpoints, the statistical analysis plan specified that the primary analysis would

include all bacteriologically-confirmed failures and recurrences (i.e. without restricting to the same strain).

In the 11 pairs of baseline and failure/recurrence isolates that were stored, same strain was defined by whole-genome-sequencing using Illumina technology on the basis of 40 single nucleotide variants between baseline and failure/recurrence isolates. All failure/recurrence isolates were within 12 single nucleotide variants of the baseline isolate (median 1 (IQR 1-6) (range 0-12)).

The secondary efficacy outcome measures were:

- time to all cause mortality up to 14 days
- time to clinically defined failure or recurrence or death by 12 weeks
- duration of bacteraemia
- 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) (all AEs reported, primary comparisons based on time to first event)
- The proportion modifying any treatment (including concomitant medications) due to drug interactions
- The proportion developing rifampicin resistant *S. aureus*
- Cost-effectiveness of rifampicin

Mortality was reported on the ARREST database on a Serious Adverse Event (SAE) electronic Case Report Form (eCRF). Clinically defined failure or recurrence was assessed clinically in the same manner as bacteriologically confirmed failure or recurrence; however, microbiological confirmation was not required (for example, patients who failed clinically but where blood cultures were not taken). Clinically defined failure/recurrence was primarily 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.

PIs were required to report all potential failures/recurrences and they were adjudicated as trial endpoints by an independent endpoint committee. The blinded independent review committee consisted of two infectious disease physicians with experience in acute/general medicine (Professor Tim Peto, Oxford; Dr Graham Cooke, Imperial; see acknowledgements). Potential

failures/recurrences were also identified through questions regarding signs and symptoms of ongoing or new *S. aureus* infection on routine case record forms, and *S. auerus* isolated from any microbiological specimen. For all such potential failures/recurrences a structured clinical narrative was completed by the site physician and approved by the site PI. All reported failures, recurrences and deaths were then adjudicated using standardised proformas by the committee without knowledge of randomised allocation.

Blood cultures were taken on days 3 and 7 following randomisation to assess duration of bacteraemia. Sensitivity to rifampicin was repeated on the day 3 and 7 blood cultures, and in all subsequent *S. aureus* isolates grown at scheduled timepoints or at failure/recurrence, in order to assess the secondary endpoint, development of rifampicin resistant *S. aureus*.

CRP was measured longitudinally as a continuous measure of response to infection.

Procedures for assessing safety

Hepatitis is the most important side effect of rifampicin. Liver function tests were performed twice whilst on rifampicin/placebo (day 3 and 10) to assess laboratory safety parameters. Additional safety blood tests or investigations were performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Grade 3 and 4 and serious adverse events were elicited at the regular clinical assessments, through consultation with the patient, their medical team, or their medical records. All such adverse events were reported on eCRFs, together with adverse events of any grade leading to modification of rifampicin/placebo dose or its interruption/early discontinuation. All adverse events (clinical and laboratory) were graded using the Common Toxicity Criteria (CTC) grading scale v3.0. SAEs were defined following the International Committee for Harmonization as events which led to death, were life-threatening, caused or prolonged hospitalisation (excluding elective procedures), caused permanent disability, or were other medical conditions or with a real, not hypothetical risk of one of the previous categories. SAEs were reported to the Medical Research Council Clinical Trial Unit at University College London (MRC CTU at UCL) according to standard timelines. All SAEs were reported on study eCRFs, unless they were specifically related to the *S. aureus* bacteraemia episode for which the

patient was originally admitted (in which case they were reported as infection-related events). The protocol specifically exempted events related to *S. aureus* bacteraemia from adverse event reporting, unless the event was fatal, to avoid double counting. The severity and likely relationship of any adverse events to rifampicin/placebo were documented by a physician. All reported adverse events were coded centrally at the MRC CTU at UCL using the Medical Dictionary for Regulatory Activities (MedDRA).

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

Procedures for assessing health related costs of *S. aureus* and quality of life

Healthcare-related costs of *S. aureus* bacteraemia in the NHS and the evaluation of health-related quality of life were evaluated using the EuroQol-5D questionnaire (EQ-5D). These assessments were used further to inform the cost effectiveness of adjunctive rifampicin and relevant antibiotic regimens for *S. aureus* bacteraemia (see Chapter 5 Economic and Health-Related Quality of life consequences of *S. aureus* bacteraemia, and effect of treatment with adjunctive rifampicin). Information on healthcare-related costs of patients in the trial was collected, 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) was collected at the regular clinical assessments, and data on other healthcare resource utilisation (post-discharge outpatient visits, medications, and procedures) was collected at the 12 week visit.

Within trial assessments of health related quality of life (using the EQ5D) were also used in the economic analysis. EQ5D scores were used to weight lifetime lived by its quality; the EQ5D tariff developed for the UK was used to derive the scores from the participants responses to the EQ5D's descriptive system. The cost effectiveness analysis thus used QALY (Quality Adjusted Life Years) as the outcome measure.

Sample Size

The trial was originally designed with two co-primary outcomes: all-cause mortality by 14 days and bacteriological failure/recurrence or death by 12 weeks. Assuming 80% power, two-sided alpha 0.025 (to adjust for multiple testing given 2 co-primary outcomes), and a 10% loss to follow-up by 12 weeks, 920 participants were needed 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. Assuming 80% power, two-sided alpha 0.025, and a lower 4% loss to follow-up by 14 days (as most participants remained in hospital over this timescale), 940 participants were needed 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 was originally therefore 940 participants.

Recruitment to the trial was slower than anticipated. To facilitate successful completion of the trial and at the request of the trial funder, after 3 years recruitment 14-day mortality was moved from a co-primary to a secondary outcome. 12-week bacteriological failure/recurrence or death therefore became the sole primary outcome with consequent decrease in sample size (due to increase in the two-sided alpha (Type I error) from 0.025 (two co-primary outcomes) to 0.05 (one primary outcome)). With 12-week bacteriological failure/recurrence or death as the sole primary outcome, the total sample size became 770 participants (alpha=0.05, other assumptions as above).

The protocol and statistical analysis plan specified that the primary outcome (bacteriologically-confirmed failure/recurrence or death) would be analysed using time-to-event methods as described below. The sample size calculation treated this outcome as binary, in order to produce a conservative estimate of sample size given uncertainties in the underlying assumptions, and since all patients were to be followed for a fixed 12 week period (that is, no additional power was gained from longer follow-up in some patients).

Statistical Methods

Randomised groups were compared followed the principle of intention-to-treat including all follow-up regardless of changes to treatment. The Statistical Analysis Plan pre-specified that any patient who was randomised in error (defined as realising that the patient should not have been randomised before taking blinded study drug and not ever taking study drug) and hence not followed up would be excluded. The blinding means that there was no possibility that knowledge of randomised allocation affected this judgement about what was an error. Any participants who were randomised in good faith (i.e. not by mistake) but never took study drug were included in all analyses.

Time-to-event analyses measured time from randomisation. Analyses of clinical outcomes censored at the earliest of 12 weeks from randomisation and the last clinical information. Analyses of mortality censored at the earliest of the timescale being considered (2 weeks, 12 weeks) or last vital status information (including that ascertained at trial closure through the National Health Service records).

The primary analyses were unstratified because the randomisation stratification factor (centre) was expected to have some small strata and participants in these strata might then not contribute to comparisons. Results from secondary stratified analyses (stratified logrank test and stratified Cox regression) were very similar (data not shown). Lost-to-follow-up was defined as not having been assessed in person or by telephone within a [-1,+8] week window of the 12 week final visit by a trial clinician and not having information on whether or not signs/symptoms of *S. aureus* were present (e.g. from the patient's General Practitioner).

Primary analysis of the primary endpoint included all randomised participants other than those considered randomised in error (following the statistical analysis plan): secondary analysis of the primary endpoint was to exclude those (expected <1%) who were subsequently identified as having had a rifampicin resistant *S. aureus* bacteraemia on susceptibility testing. As no patients were identified after randomisation as having had a rifampicin resistant *S. aureus* bacteraemia at enrolment, this analysis was identical to the primary analysis. In the statistical analysis plan (but not the protocol), a per-protocol analysis was also specified for the primary

endpoint, including all participants in the primary intention-to-treat analysis who received active/placebo for ≥80% of days from start of trial drug to earliest of: 14 days subsequently/death/discontinuation of active antibiotics (not including trial drug).

Safety analyses included all data between randomisation and 12 weeks post-randomisation (inclusive). Non-fatal events related to S. aureus bacteraemia were not considered AEs/SAEs in the protocol.

Where composite outcomes did not include all-cause mortality as part of the composite, competing risks analysis methods were used. Analogous to a Kaplan-Meier estimate, competing risks methods use cumulative incidence functions to estimate the probability of the event. We estimated the effect of randomised group on the subdistribution hazard that corresponds to this cumulative incidence function. Stratification is not possible with the estimating equation approach used to estimate these subdistribution hazards and so these analyses were conducted unstratified.

CRP and liver function test results were compared between randomised groups over time using generalised estimating equations (GEE) (normal distribution, independent correlation structure) with randomised group, adjusting for the stratification factor, baseline values and scheduled visit week as categorical independent variables and interaction between baseline values and scheduled visit week. The closest measurement to each scheduled visit date within equally spaced windows was used as the measurement at each scheduled visit. The midpoint between two scheduled assessment days was taken as belonging to the latter window. Where there were two values within one of these equally spaced windows, but both equidistant from the nominal assessment day, the later value was used. Analyses were based on observed data. To account for CRP values above limit of quantification in one centre (that is, CRP only reported as >156 mg/L if above this threshold), mean CRP was estimated using normal interval regression. For analyses of change from baseline, these values were assumed equal to the limit of quantification.

For blood cultures, baseline (used to define baseline resistance/susceptibility) was defined as the closest up to and including day 0, and up to one day post-randomisation providing this was on or before date of start of trial drug. Cultures prior to randomisation were used in preference to cultures the same number of days after randomisation, but on or before the date of start of

trial drug. As eligibility was based on the screening positive blood culture, and because the intention was to characterise persisting bacteraemia, baseline bacteraemia included cultures on day-one where a culture on the day of or on the day prior to randomisation was not available. For duration of bacteraemia, baseline was defined as the closest up to and including day 0 within the preceding day, and up to one day post-randomisation.

For laboratory measurements (e.g. CRP), baseline was defined as the closest up to and including day 0 within the preceding 4 days, and up to one day post-randomisation providing this was on or before date of start of trial drug. Measurements prior to randomisation were used in preference to measurements the same number of days after randomisation, but on or before the date of start of trial drug.

A deep infection focus was defined as infection of implanted vascular device, native/prosthetic heart value, native/prosthetic bone/joint, or deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection).

Information on all antibiotics received through 12 weeks was collected, but not according to specific indication. Primary antibiotic treatment, and its duration, was therefore defined by complete cessation of all antibiotics for 2 days, with the exception of vancomycin where intermittent dosing up to 1 week was allowed. The cessation of vancomycin was defined by adding the number of days between the last two doses to the date of the final dose.

SUBGROUP ANALYSES

Subgroup analyses were conducted to assess consistency of effects across different participant characteristics. The primary method of assessing subgroup effects was an interaction test within a Cox proportional hazards regression. For the continuous factors we used both categorisation and natural cubic splines (five knots at the 10th, 25th, 50th, 75th, and 90th centiles; four knots at the 10th, 33rd, 67th, and 90th centiles for Charlson comorbidity index score (as 10th and 25th centiles identical)) to test for interactions. Subgroup analyses were conducted unstratified to avoid losing information from small strata with no events in one randomised group. No formal adjustment for multiple testing was made for subgroup analyses.

We pre-specified in the protocol twelve subgroup analyses for the primary endpoint; namely 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 trial drug only or regimen containing IV trial 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, age and CRP (terciles).

The statistical analysis plan included 6 additional subgroup analyses, but prioritised the subgroup analyses as follows (*=in protocol).

1. *Time from initiation of first active antibiotic treatment to initiation of randomised treatment (0-24, >24-48, >48-72, >72 hours)
1. *Class of initial antibiotic treatment, and according to individual drugs where these are used by >10% of the trial population
1. *MRSA/MSSA
1. *IV catheter (central/peripheral venous line)/implanted vascular device-associated infection vs other (based on portal of entry)
1. *Deep focus (implanted vascular device, native/prosthetic heart valve, native/prosthetic joint, deep tissue infection/abscess)/no deep focus (based on foci of infection)
1. *Endocarditis (main focus/foci of infection at time first positive blood culture taken = native heart valve/prosthetic heart valve)/no endocarditis
1. *Foci of infection known/not known
1. *Age (terciles)
2. *Initial oral randomised treatment frequency (once vs twice daily)
2. *Initial treatment with oral trial drug only or regimen containing IV trial drug
2. *Whether gentamicin was administered between first positive blood culture and 48 hours post-randomisation, regardless of activity
2. Whether any active antibiotic other than that first administered (excluding trial drug), trial drug and gentamicin was administered between first positive blood culture and 48 hours post-randomisation (yes vs no)
2. *Baseline CRP (terciles)
2. Charlson comorbidity index score (0, 1-2, 3-4, ≥5)
3. Time from randomisation to initiation of randomised treatment (0-4, >4-12, >12-24, >24 hours)

3. Community, healthcare associated and nosocomial acquisition
3. Calendar year of randomisation
3. Baseline neutrophils (terciles)

We also considered additional exploratory subgroups defined by initial total daily dose (600 vs 900 mg), and whether or not the patient was bacteraemic at randomisation, leading to 20 subgroups in total.

Data Collection and Handling

Data was entered by staff at each NHS Trust Hospital on to eCRFs on the online ARREST trial database. Staff with data entry responsibilities were required to complete database training before they were granted access to the database. Data was exported into Stata (v14.2) (StataCorp LP, College Station, TX, USA) for analysis.

Interim Analyses

The trial was reviewed by the ARREST Data Monitoring Committee (DMC). They met four times in strict confidence over the course of the trial: 14 November 2013, 31 October 2014, 26 May 2015, 24 February 2016. DMC reccommendations were communicated through a letter to the TSC following each meeting.

Clinical Site Monitoring

Trial monitoring was carried out according to the protocol. Trial centres agreed to provide access to source data and consent was gained from patients for direct access to patient notes. All centres that had a minimum of 4 patients that had completed follow-up (week 12 visit or death) were monitored on-site at least once during the trial. The following data were validated from source documents:

- eligibility and signed consent
- trial drug and antibiotic management

- safety events
- any data concerns raised by central monitoring

Patient and Public Involvement

The ARREST trial was developed with the Healthcare-associated Infection Service Users Research Forum (SURF: www.hcaisurf.org); in particular Jennifer Bostock who was the Patient and Public Involvement (PPI) representative on the ARREST Trial Steering Committee. Ms Bostock advised on the inclusion of incapacitated adults, the application of the Mental Capacity Act, and on the information provided to patients. SURF is no longer active, but Ms Bostock is helping disseminate the trial's results beyond the academic and healthcare professional community to other patient groups that she works with including MRSA Action UK.

In particular, given recruitment challenges, Ms Bostock developed and led the sub-study investigating patients' and carers' reasons for and for not participating in the trial. This is reported in full in Chapter 4 Trial Participation Qualitative Sub-study.

Protocol Changes

The trial was approved by the London (Westminster) Research Ethics Committee (12/LO/0637). See **Appendix 1** for changes to the protocol.

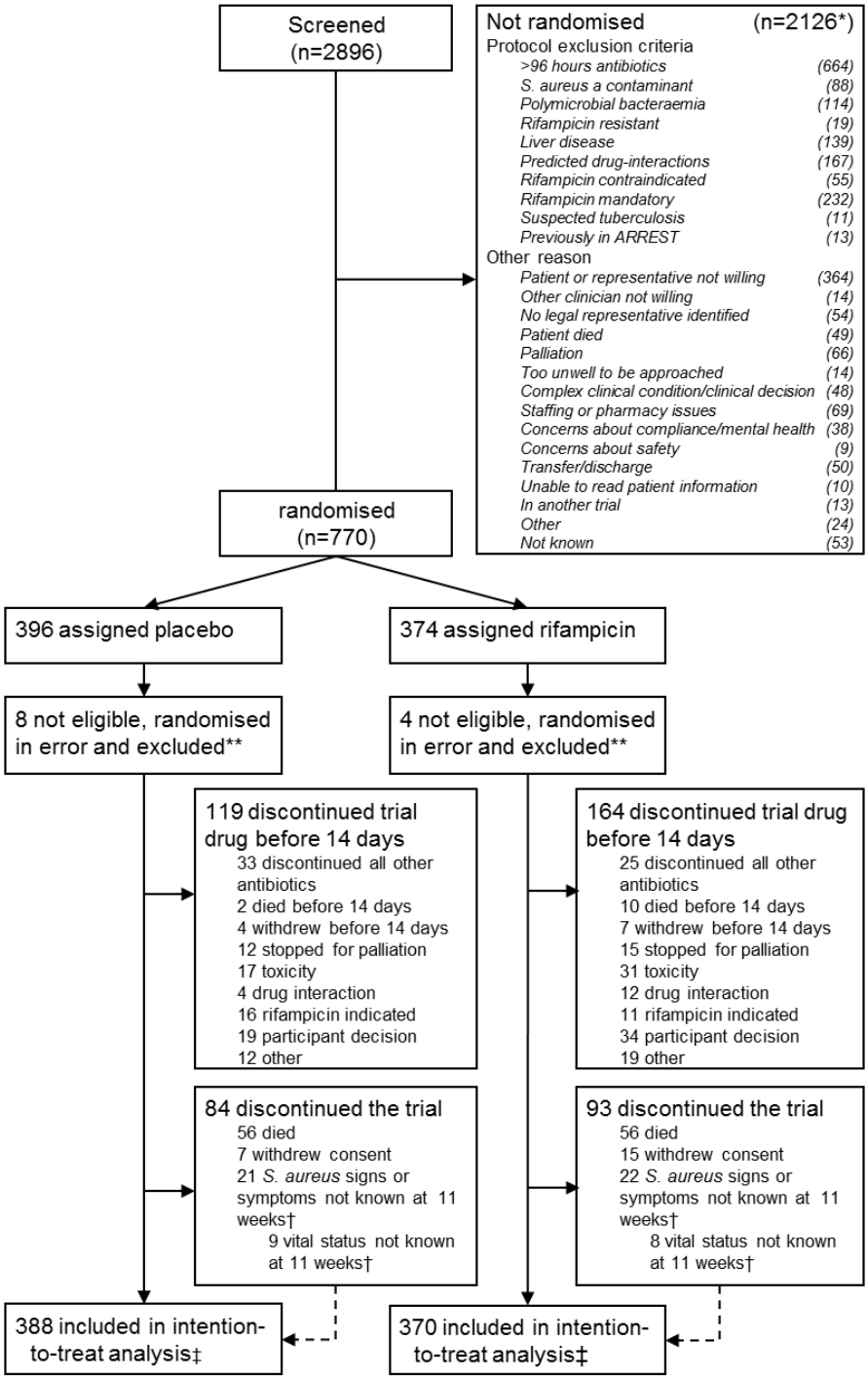
Chapter 3 Results

Participant flow diagram

Between 10th December 2012 and 25th October 2016, 770 participants from 29 United Kingdom hospital groups were randomised to add placebo (n=396) or rifampicin (n=374) to their 'backbone' antibiotic treatment (**Figure 2**). 2896 were screened for entry to the trial. The most common reason for not randomising a potentially eligible participant was that they had already received >96 hours of antibiotics (n=664). In 364 cases the participant was not willing. Rifampicin was considered mandatory in 232 cases. Known rifampicin resistance occurred in only 19 cases. However 139 cases were not eligible because of pre-existing liver disease raising concerns about rifampicin treatment and 167 cases because of predicted drug interactions.

12 (8 placebo; 4 rifampicin) were randomised in error (the participant should not have been randomised and never received trial drug) and were excluded following the Statistical Analysis Plan. Of these 12 participants, seven participants had predicted drug-interactions, two were misdiagnosed (*S. aureus* was not grown from blood), rifampicin was considered mandatory in one patient, one other clinician considered that the participant should not have been randomised due to acute kidney injury, one other clinician considered participant should not have been randomised as they were in another study (not of an investigational medicinal product, allowed according to the protocol).

Thus 758 (388 placebo, 370 rifampicin) participants were included in the analyses. The median (IQR) [range] number of patients recruited per centre was 11 (4-30) [1-163]. 415 (54.7%) participants were recruited from five centres (Oxford n=163, Guy's and St Thomas's n=99, Liverpool n=62, Plymouth n=48 and Sheffield n=43). The large number of centres recruiting small numbers of participants together with the relatively large block size (6-8) led to a small imbalance in the numbers included randomised to placebo (n=388) and rifampicin (n=370).



* reasons are not mutually exclusive, therefore total is more than the number of participants not randomised

** 7 participants with predicted drug-interaction, 2 misdiagnosed (*S. aureus* not grown from blood but only other samples), rifampicin considered mandatory in 1, 1 other clinician considered participant should not have been randomised due to acute kidney injury, 1 other clinician considered participant should not have been randomised as they were in another study (not of an investigational medicinal product)

† Final 12 week visit could occur any time from 11 weeks onwards according to the protocol. Consent withdrawals not included in these numbers

‡ Time-to-event analyses included all time at risk from randomisation to the earliest of the event or last clinical follow-up if the event had not occurred.

Figure 2: Participant flow diagram

Baseline characteristics

Baseline characteristics were well-balanced between randomised groups (**Table 1, Table 2**).

495 (65.3%) participants were men (**Table 1**). They were aged median (interquartile range (IQR)) 65 (50-76) years, weighed 76.0 kg (64.0-90.0) and had median Charlson co-morbidity score 2 (0-3). Diabetes (30.1%), renal disease (18.2%), cancer (16.6%) and chronic lung disease (11.9%) were all common co-morbidities. 83 (10.9%) were active injecting drug users. 70 (9.2%) participants were in an intensive care unit, and 90 (11.9%) had had surgery in the last 30 days. 127 (16.8%) had consent provided by a legal representative due to incapacity. Reflecting disease severity, mean (Standard Error) CRP was 164 (3.7) mg/L and median (IQR) Sequential Organ Failure Assessment (SOFA) score was 2 (1-4).

At randomisation, participants had already received a median (IQR) 62 (42-75) hours of active antibiotics, with their first blood culture taken a median (IQR) 3 (2-3) days previously and their first symptoms occurring a median (IQR) 4 (3-6) days previously. 157/642 (24.5%) still had a positive blood culture on the day of randomisation.

485 (64.0%) infections were community-acquired, with only 132 (17.4%) nosocomial; 47 (6.2%) were caused by methicillin-resistant *S. aureus* (MRSA). No patients were known to have rifampicin-resistant *S. aureus* bacteraemia at randomisation.

The initial focus was deep in 301 (39.7%), including 33 (4.4%) with endocarditis and 14 (1.8%) with infected prostheses; 130 (17.2%) were due to infected central/peripheral lines; 138 (18.2%) associated with skin/soft tissue infections; another type of focus was identified in 49 (6.5%) and not established in 139 (18.3%).

In 255 (33.6%) participants the most likely portal of entry of *S. aureus* into the bloodstream was a clinically apparent skin or soft tissue infection unrelated to a surgical intervention. Central or peripheral lines were the most likely portal of entry in 141 (18.6%) participants, although 191 (25.7%) had a vascular catheter in situ at randomisation. For 218 (18.6%) participants the portal of entry was unknown.

Table 1 Participant characteristics at randomisation

Factor	Placebo N=388	Rifampicin N=370*	Total N=758*
Male	246 (63.4%)	249 (67.3%)	495 (65.3%)
Age at last birthday (years)	66 (51, 76)	64 (49, 76)	65 (50, 76)
Charlson comorbidity score*	2 (0, 3)	1 (0, 3)	2 (0, 3)
Cancer (N=756)	60 (15.5%)	66 (17.8%)	126 (16.6%)
Chronic lung disease (N=756)	42 (10.8%)	48 (13.0%)	90 (11.9%)
Congestive heart disease (N=756)	40 (10.3%)	42 (11.4%)	82 (10.8%)
Moderate or severe liver disease (N=755)	5 (1.3%)	5 (1.4%)	10 (1.3%)
Moderate or severe renal disease (N=755)	80 (20.6%)	58 (15.7%)	138 (18.2%)
Diabetes*	119 (30.7%)	109 (29.5%)	228 (30.1%)
Active injecting drug use (N=751)	41 (10.6%)	42 (11.4%)	83 (10.9%)
Weight (N=755)	76.0 (65.0, 90.0)	76.0 (64.0, 89.0)	76.0 (64.0, 90.0)
Admitted to ICU *	36 (9.3%)	34 (9.2%)	70 (9.2%)
CRP (mg/L) (N=755) **	163 (5.2)	166 (5.3)	164 (3.7)
White cell count (10^9/L) (N=752)	9.5 (6.7, 13.4)	9.5 (7.1, 13.1)	9.5 (6.9, 13.2)
Neutrophil count (10^9/L) (N=752)	7.3 (4.7, 11.0)	7.4 (4.9, 10.7)	7.3 (4.8, 10.9)
Lymphocyte count (10^9/L) (N=751)	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)
SOFA score*	2 (1, 4)	2 (1, 4)	2 (1, 4)
Vascular catheter in situ (N=744)	102 (26.8%)	89 (24.5%)	191 (25.7%)
Surgery in the last 30 days (N=756)	53 (13.7%)	37 (10.1%)	90 (11.9%)
Days between first new symptom caused by *S. aureus* and randomisation and randomisation*	4 (3, 6)	4 (3, 6)	4 (3, 6)
Days between drawing of first positive blood culture and randomisation*	3 (2, 3)	3 (2, 4)	3 (2, 3)
Hours of active antibiotic therapy before randomisation	63 (42, 75)	60 (41, 76)	62 (42, 75)
Blood culture positive at randomisation	69/326 (21.2%)	88/316 (27.8%)	157/642 (24.5%)

* One rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant. If any other participants had missing data, then denominators are shown.
** Mean (SE) estimated using normal interval regression to account for values above limit of quantification in one centre.
Note: showing n(%) for categorical factors, or median (IQR) for continuous factors other than CRP where mean(SE) is shown.

Table 2 Infection characteristics at randomisation

Factor	Placebo N=388	Rifampicin N=370*	Total N=758*
Mode of acquisition of infection*			
Community acquired	240 (61.9%)	245 (66.2%)	485 (64.0%)
Nosocomial infection (onset ≥48 hrs after admission)	76 (19.6%)	56 (15.1%)	132 (17.4%)
Healthcare associated (all other)	72 (18.6%)	68 (18.4%)	140 (18.5%)
MRSA	21 (5.4%)	26 (7.0%)	47 (6.2%)
Rifampicin-resistant infection at randomisation (N=750) ††	0	0	0
Main focus/foci of infection *†			
Native heart valve	16 (4.1%)	17 (4.6%)	33 (4.4%)
Native joint	34 (8.8%)	29 (7.8%)	63 (8.3%)
Prosthetic heart valve/joint **	5 (1.3%)	9 (2.4%)	14 (1.8%)
Implanted vascular device (other than intravenous catheter)	23 (5.9%)	13 (3.5%)	36 (4.7%)
Deep tissue infection/abscess	94 (24.2%)	82 (22.2%)	176 (23.2%)
Central or peripheral intravenous catheter	67 (17.3%)	63 (17.0%)	130 (17.2%)
Skin/soft tissue (excluding wounds)	66 (17.0%)	72 (19.5%)	138 (18.2%)
Surgical wound	15 (3.9%)	10 (2.7%)	25 (3.3%)
Pneumonia or urinary tract infection	30 (7.7%)	30 (8.1%)	60 (7.9%)
Not established	67 (17.3%)	72 (19.5%)	139 (18.3%)
Any deep-seated focus ‡	159 (41.0%)	142 (38.4%)	301 (39.7%)
Likely portal of entry of *S. aureus* into the bloodstream†			
Clinically apparent skin or soft tissue infection unrelated to a surgical intervention	131 (33.8%)	124 (33.5%)	255 (33.6%)
Infected surgical wound within last 3 months, with or without associated prosthesis	19 (4.9%)	19 (5.1%)	38 (5.0%)
Peripheral vascular catheter (including arterial line)	23 (5.9%)	26 (7.0%)	49 (6.5%)
Central vascular catheter (including PICC line)	50 (12.9%)	42 (11.4%)	92 (12.1%)
Other implanted vascular device (e.g. pacemaker, stent, graft)	15 (3.9%)	12 (3.2%)	27 (3.6%)
Respiratory	16 (4.1%)	13 (3.5%)	29 (3.8%)
Per-urethral or supra-pubic urinary catheter	7 (1.8%)	8 (2.2%)	15 (2.0%)
Recent (within 1 week of bacteraemia) urological surgery	1 (0.3%)	3 (0.8%)	4 (0.5%)
Not known (absence of any of the above)	110 (28.4%)	108 (29.2%)	218 (28.8%)
Injecting drug user	8 (2.1%)	9 (2.4%)	17 (2.2%)
Corticosteroid Injection Into Joint	4 (1.0%)	2 (0.5%)	6 (0.8%)
Other	2 (0.5%)	3 (0.8%)	5 (0.7%)
Not completed (missing data)	2 (0.5%)	1 (0.3%)	3 (0.4%)

* One rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant.
† Individuals could have multiple foci, and portal of entry,, so sum is more than total randomised
** 2 placebo, 5 rifampicin with prosthetic heart valves; 3 placebo, 4 rifampicin with prosthetic joints.
‡ Infection of implanted vascular device, native/prosthetic heart value, native/prosthetic bone/joint, deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection).
†† Not required to be known at the point of randomisation for eligibility.
Note: showing n(%) for categorical factors, or median (IQR) for continuous factors.

Follow-up and treatment received

Overall completeness of scheduled visits was high up to 14 days. Excluding visits after death or discharge, day-3 visits were missed in 10/372 (2.7%) placebo versus 12/350 (3.4%) rifampicin participants, day-7 visits were missed in 15/337 (4.5%) placebo versus 16/311 (5.1%) rifampicin participants, day-10 visits were missed in 22/293 (7.5%) placebo versus 26/262 (9.9%) rifampicin participants, and day-14 visits were missed in 9/230 (3.9%) placebo versus 13/204 (6.4%) rifampicin participants. Completeness dropped after 14 days when patients started to be discharged, for example visits were missed in 21/149 (14.1%) placebo versus 19/134 (14.2%) rifampicin participants at day-21; 23/115 (20.0%) placebo versus 23/93 (24.7%) rifampicin participants at day-28; and 25/89 (28.1%) placebo versus 19/58 (32.8%) rifampicin participants at day-35.

22 (2.9%) participants withdrew consent. At the 12-week visit, only 39 (5.1%) had unknown vital status and 65 (8.6%) were not assessed for signs/symptoms of *S. aureus* infection (including consent withdrawals).

23 (3.0%) participants were still in hospital at 12-weeks (15 (3.9%) placebo versus 8 (2.2%) rifampicin, p=0.17). The median (IQR) initial hospitalisation duration was 21 (14-50) versus 22 (13-43) days in placebo and rifampicin groups respectively (p=0.80) (**Figure 3**). 132 (39.8%) placebo versus 138 (44.8%) rifampicin participants were discharged on outpatient parental therapy (p=0.35). 94 (24.2%) placebo versus 83 (22.4%) rifampicin participants were re-admitted post-discharge and before 12-weeks (p=0.56), spending a median (IQR) 9 (4-20) and 10 (3-20) nights in hospital post-original-discharge respectively. Any admission was considered for reasons relating to *S. aureus* bacteraemia in 16 (4.1%) placebo and 9 (2.4%) rifampicin participants (p=0.19).

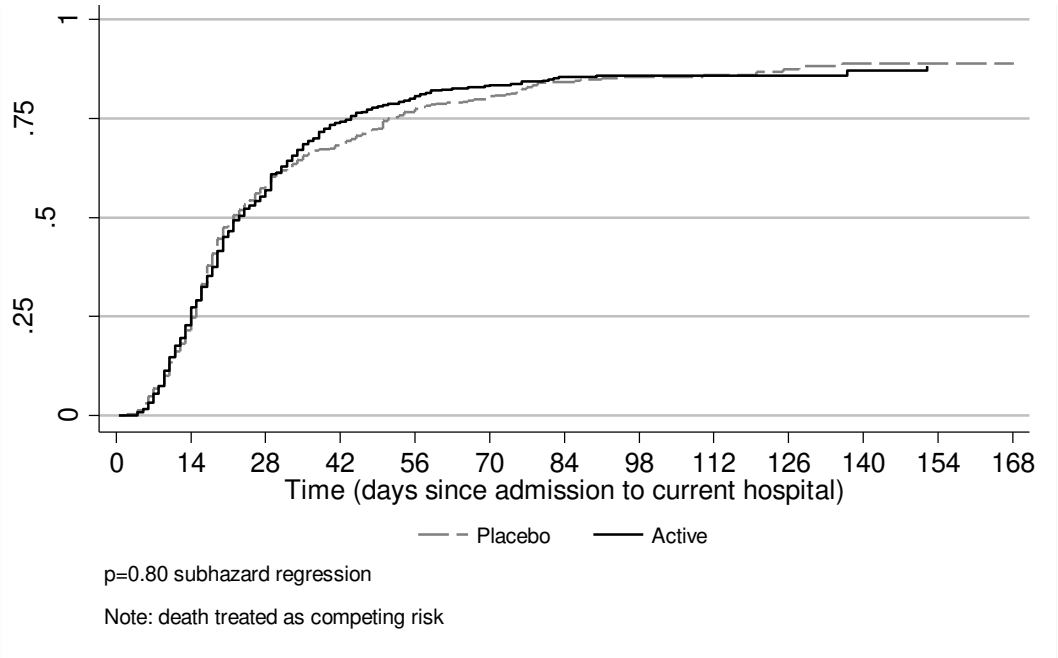


Figure 3 Days from admission to current hospital and original post-randomisation discharge

744 (98.2%) participants initiated blinded trial drug, a median (IQR) 4.3 (2.3-7.8) hours after randomisation. Reasons for not initiating blinded trial drug were patient decision (n=7); increasing liver enzyme levels (2); started on open-label rifampicin (2); withdrawn for palliation (1); incorrectly believed that the bacteraemia was rifampicin resistant (1); and unable to access IV trial drug from trials pharmacy at weekend (1).

96 (12.7%) initiated IV trial drug rather than oral trial drug (

Table 3). 595 (78.5%) initiated 900mg daily rather than 600 mg daily and 362 (52.2%) twice-daily rather than once-daily. The median (IQR) dose was 11.1 (10.0-12.9) mg/kg. Trial drug was initiated a median (IQR) 68 (48-85) hours after starting active antibiotics for the current infection. Trial drug was continued for median (IQR) 12.6 (6.0-13.2) days in rifampicin participants versus 13.0 (11.3-13.5) days in placebo participants ($p<0.0001$; primarily due to antibiotic-modifying AEs and drug-drug interactions, see below). 60 (15.5%) placebo versus 51 (15.6%) rifampicin participants ever received IV trial drug. Percentages reporting missing any doses of trial drug ranged from 9.5%-16.2% but did not differ between randomised groups (**Figure 4**; global $p=0.71$).

Table 3 Trial drug treatment

Factor	Placebo N=388	Rifampicin N=370	**Total N=758**
Never initiated trial drug	8 (2.1%)	6 (1.6%)	14 (1.8%)
Initiated IV trial drug	51 (13.1%)	45 (12.2%)	96 (12.7%)
Initiated oral trial drug	329 (84.8%)	319 (86.2%)	648 (85.5%)
Initiated trial drug once-daily	175 (45.1%)	173 (46.8%)	348 (45.9%)
Initiated trial drug twice-daily	205 (52.8%)	191 (51.6%)	396 (52.2%)
Initiated trial drug 600mg daily	74 (19.1%)	75 (20.3%)	149 (19.7%)
Initiated trial drug 900mg daily	306 (78.9%)	289 (78.1%)	595 (78.5%)
Initial total daily dose (mg/kg) (N=741)	11.2 (9.9, 12.9)	11.0 (10.0, 12.7)	11.1 (10.0, 12.9)
Hours from starting active antibiotics to starting trial drug	69 (49, 85)	68 (46, 85)	68 (48, 85)
Hours from randomisation to initiation of randomised treatment	4.2 (2.3, 7.6)	4.3 (2.3, 8.0)	4.3 (2.3, 7.8)
Days on trial drug	13.0 (11.3, 13.5)	12.6 (6.0, 13.2)	12.8 (7.9, 13.4)
Total duration of study drug (days)			
0	8 (2.1%)	6 (1.6%)	14 (1.8%)
<3	18 (4.6%)	22 (5.9%)	40 (5.3%)
3-5	28 (7.2%)	57 (15.4%)	85 (11.2%)
6-9	24 (6.2%)	43 (11.6%)	67 (8.8%)
10-13	49 (12.6%)	42 (11.4%)	91 (12.0%)
14	255 (65.7%)	197 (53.2%)	452 (59.6%)
>14	6 (1.5%)	3 (0.8%)	9 (1.2%)
Ever received IV trial drug	60 (15.5%)	56 (15.1%)	116 (15.3%)

Note: showing n(%) or median (IQR).

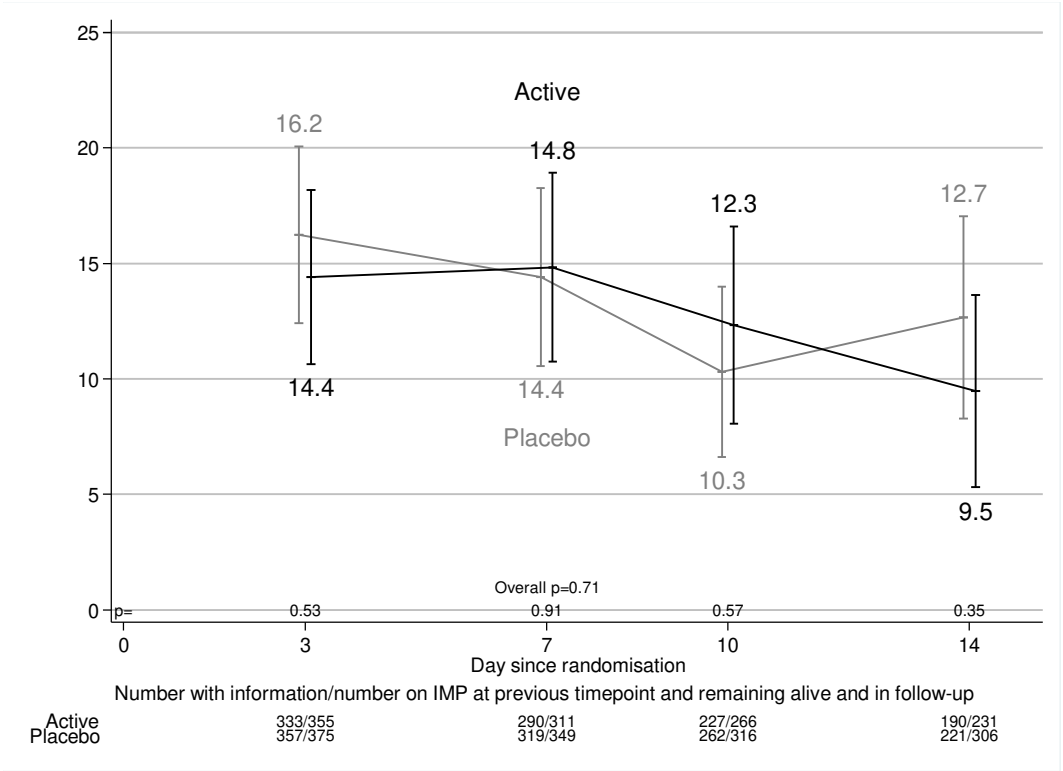


Figure 4 Percentage reporting missing one or more doses of trial drugs since the previous scheduled visit

A substantial variety of 'backbone' active antibiotics were used (**Table 4;** details in **Table 26** in **Appendix 2**). Flucloxacillin was given in 619 (81.7%) participants, and vancomycin or teicoplanin in 380 (50.1%) participants at some point in the primary treatment course, with no evidence of difference between randomised groups (p=0.44 and p=0.34, respectively). Stat (one-off) doses of gentamicin or amikacin were used in 199 (26.3%) participants (p=0.89). There was no evidence that the numbers of antibiotics used (median (IQR) 3 (2-4)) or the total duration of active anti-staphylococcal treatment (including therapy received before randomisation) (median (IQR) 29 (18-45) days) differed between groups (p=0.98 and 0.64 respectively) (**Table 4**). Post-randomisation active anti-staphylococcal treatment was taken for median (IQR) 27 (15-41) days in placebo vs 26 (15-43) days in rifampicin participants.

32 (8.6%) rifampicin participants versus 52 (13.4%) placebo participants used open-label rifampicin at some point after randomisation (p=0.04). Median time from randomisation to initiation of open-label rifampicin was 14 days (IQR 7-18) (**Table 4**). There was a trend to slightly fewer participants initiating open-label rifampicin from 14 days onwards (i.e. after stopping trial drug; 14 (3.8%) vs 27 (7.0%) placebo, p=0.053). Open-label rifampicin was used in participants with a range of original infection foci (**Table 5**). The median (IQR) duration of open-label rifampicin was 25 days (13-45) in placebo vs 32 (26-48) in rifampicin participants.

60 (15.5%) placebo participants received antibiotics after the primary course versus 34 (9.2%) rifampicin participants (p=0.01).

Table 4 'Backbone' antibiotic treatment

Factor	Placebo N=388	Rifampicin N=370	**Total N=758**
'Backbone' active antibiotic treatment*			
Flucloxacillin	321 (82.7%)	298 (80.5%)	619 (81.7%)
Co-amoxiclavulante	122 (31.4%)	107 (28.9%)	229 (30.2%)
Piperacillin/tazobactam	115 (29.6%)	102 (27.6%)	217 (28.6%)
Vancomycin/teicoplanin	188 (48.5%)	192 (51.9%)	380 (50.1%)
Cephalosporin	110 (28.4%)	104 (28.1%)	214 (28.2%)
Fluoroquinolone	47 (12.1%)	46 (12.4%)	93 (12.3%)
Macrolide	30 (7.7%)	28 (7.6%)	58 (7.7%)
Clindamycin	23 (5.9%)	36 (9.7%)	59 (7.8%)
Tetracycline	29 (7.5%)	26 (7.0%)	55 (7.3%)
Gentamicin/amikacin	101 (26.0%)	98 (26.5%)	199 (26.3%)
Stat gentamicin/amikacin	95 (24.5%)	87 (23.5%)	182 (24.0%)
Carbapenem	38 (9.8%)	35 (9.5%)	73 (9.6%)
Other antibiotic**	52 (13.4%)	52 (14.1%)	104 (13.7%)
Number of antibiotics received during *S. aureus* infection episode (excluding study drug)	3 (2, 4)	3 (2, 4)	3 (2, 4)
Days of antibiotic treatment for *S. aureus* infection episode (days)	30 (18-44)	29 (17-45)	29 (18-45)
Rifampicin used open-label	52 (13.4%)	32 (8.6%)	84 (11.1%)
Initiated <14 days from randomisation†	25 (6.4%)	18 (4.9%)	43 (5.7%)
Initiated ≥14 days from randomisation	27 (7.0%)	14 (3.8%)	41 (5.4%)

* including active antibiotics taken from the first blood culture sample throughout the illness episode
** excluding open-label rifampicin
† that is, blinded trial drug stopped and open-label rifampicin initiated for clinical reasons.
Note: showing n(%) or median (IQR).

Table 5 Initial infection focus in participants who received open-label rifampicin at any point during 12 weeks follow-up

Infection focus	Placebo N=52	Rifampicin N=32	Total N=84
Central venous line (including picc line)	1 (1.9%)	2 (6.3%)	3 (3.6%)
Implanted vascular device (e.g. pacemaker, stent, graft)	8 (15.4%)	0 (0.0%)	8 (9.5%)
Infected intravascular thrombus	2 (3.8%)	3 (9.4%)	5 (6.0%)
Native heart valve	6 (11.5%)	2 (6.3%)	8 (9.5%)
Prosthetic heart valve	1 (1.9%)	2 (6.3%)	3 (3.6%)
Native joint	1 (1.9%)	5 (15.6%)	6 (7.1%)
Prosthetic joint	0 (0.0%)	1 (3.1%)	1 (1.2%)
Vertebral bone/disc	13 (25.0%)	8 (25.0%)	21 (25.0%)
Epidural or intraspinal empyema	4 (7.7%)	1 (3.1%)	5 (6.0%)
Deep tissue infection or abscess	6 (11.5%)	3 (9.4%)	9 (10.7%)
Surgical wound	3 (5.8%)	0 (0.0%)	3 (3.6%)
Skin/Soft tissue (excluding wounds)	6 (11.5%)	3 (9.4%)	9 (10.7%)
Pneumonia	2 (3.8%)	1 (3.1%)	3 (3.6%)
Other ‡	6 (11.5%)	0 (0.0%)	6 (7.1%)
Not established	6 (11.5%)	9 (28.1%)	15 (17.9%)

‡ Central nervous system (n=2, both placebo); osteomyelitis (n=1, placebo); Urinary tract (n=3, all placebo)

159 placebo versus 142 rifampicin participants had a deep focus which was drained/removed in 35 (22.0%) versus 29 (20.4%), a median (IQR) 5 (2-12) and 3 (1-6) days from randomisation respectively (**Table 6**). 88 placebo versus 76 rifampicin participants had an intra-vascular device which was removed in 62 (70.5%) versus 60 (78.9%), a median (IQR) 2 (0-3) and 1 (0-2) days prior to randomisation respectively.

Table 6 Infection focus management

Factor	Placebo N=388	Rifampicin N=370	Total N=758
Any deep-seated focus *	159	142	301
Drained/removed	35 (22.0%)	29 (20.4%)	64 (21.3%)
Median days from randomisation to drainage/removal (IQR)	5 (2, 12)	3 (1, 6)	4 (2, 10)
Not removed	118 (74.2%)	109 (76.8%)	227 (75.4%)
Not known	6 (3.8%)	4 (2.8%)	10 (3.3%)
Non-device related focus	233	222	455
Drained/removed	39 (16.7%)	36 (16.2%)	75 (16.5%)
Median days from randomisation to drainage/removal (IQR)	4 (2, 11)	4 (2, 8)	4 (2, 10)
Not removed	187 (80.3%)	179 (80.6%)	366 (80.4%)
Not known	7 (3.0%)	7 (3.2%)	14 (3.1%)
Intra-vascular device	88	76	164
Removed	62 (70.5%)	60 (78.9%)	122 (74.4%)
Median days from randomisation to removal (IQR)	-2 (-3, 0)	-1 (-2, 0)	-1 (-2, 0)
Not removed	25 (28.4%)	15 (19.7%)	40 (24.4%)
Not known	1 (1.1%)	1 (1.3%)	2 (1.2%)
Non-vascular prosthetic implant/device	5	9	14
Removed	0 (0.0%)	2 (22.2%)	2 (14.3%)
Median days from randomisation to removal (IQR)	-	7 (2, 11)	7 (2, 11)
Not removed	5 (100.0%)	7 (77.8%)	12 (85.7%)

* Infection of implanted vascular device, native/prosthetic heart value, native/prosthetic bone/joint, deep tissue infection/abscess (including vertebral bone/disc or other bone infection, epidural or intraspinal empyema, infected intravascular thrombus, brain infection).

UNBLINDING AND BLINDING ASSESSMENT

At least one individual was unblinded for 14 participants (9 rifampicin, 5 placebo). In two cases this was only of a non-trial physician and ward pharmacist respectively, for participant safety. In three further cases this was of the research nurse only, but no other members of the clinical or research teams.

At the final 12 week visit, physicians and participants were asked which treatment they believed they had received. 203/243 (83.5%) physicians of participants randomised to rifampicin reported that they genuinely had no idea versus 249/279 (89.2%) placebo (p=0.08).

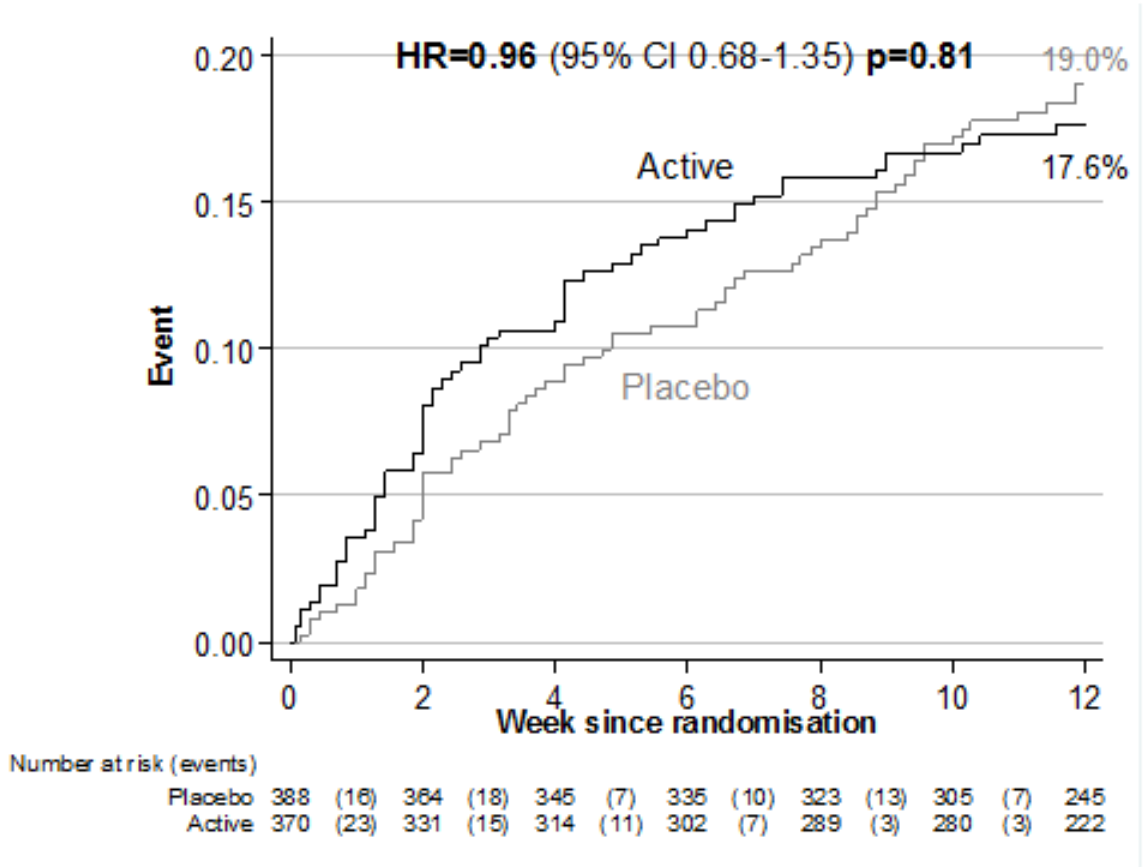
32 (13.2%) and 17 (6.1%) respectively guessed the correct allocation. In contrast, 113/199 (56.8%) participants randomised to rifampicin reported that they genuinely had no idea versus 159/229 (69.4%) placebo (p=0.007). 72 (36.2%) and 35 (15.3%) respectively guessed the correct allocation.

Primary endpoint

By 12-weeks, bacteriological failure/recurrence or death occurred in 62 (16.8%) rifampicin versus 71 (18.3%) placebo participants (absolute risk difference (RD) = -1.4% (95% CI -7.0%, +4.3%); hazard ratio (HR) = 0.96 (0.68-1.35) p=0.81, **Figure 5A**). In exploratory post-hoc analyses, comparing rifampicin with placebo there were 4 (1.1%) versus 5 (1.3%) failures (competing-risks p=0.82), 3 (0.8%) versus 16 (4.1%) recurrences (competing-risks p=0.01), and 55 (14.9%) versus 50 (12.9%) deaths without bacteriological failure/recurrence respectively (competing-risks p=0.30) (**Table 7**). The number-needed-to-treat to prevent one bacteriologically-confirmed recurrence was 29.

242 (65.4%) rifampicin versus 290 (74.7%) placebo were included in the per-protocol population (received active rifampicin/placebo for ≥80% of days from start of trial drug to earliest of: 14 days subsequently/death/discontinuation of active antibiotics (not including trial drug)). By 12 weeks, 39 (16.1%) rifampicin versus 49 (16.9%) placebo experienced bacteriological failure/recurrence or died (absolute risk difference (RD) = -0.8% (95% CI –7.3, +5.6); hazard ratio (HR) = 1.00 (0.65-1.52) p=0.99). An exploratory post-hoc analysis was also done additionally excluding participants in either group who started open-label rifampicin at any time during follow-up. 225 (60.1%) rifampicin versus 262 (67.5%) placebo were included in this post-hoc per-protocol population. By 12 weeks, 37 (16.4%) rifampicin versus 37 (14.1%) placebo experienced bacteriological failure/recurrence or died (absolute risk difference (RD) = +2.3% (95% CI –4.3, +8.8); hazard ratio (HR) =1.23 (0.78-1.93) p=0.38).

Of 28 failures/recurrences where *S. aureus* was isolated from a sterile site, paired baseline and failure/recurrence isolates were stored for 11 (39%). All failure/recurrence isolates were whole genome sequenced and within 12 single nucleotide variants of the baseline isolate (median 1 (IQR 1-6) (range 0-12)).



(b) Three priority subgroup analyses

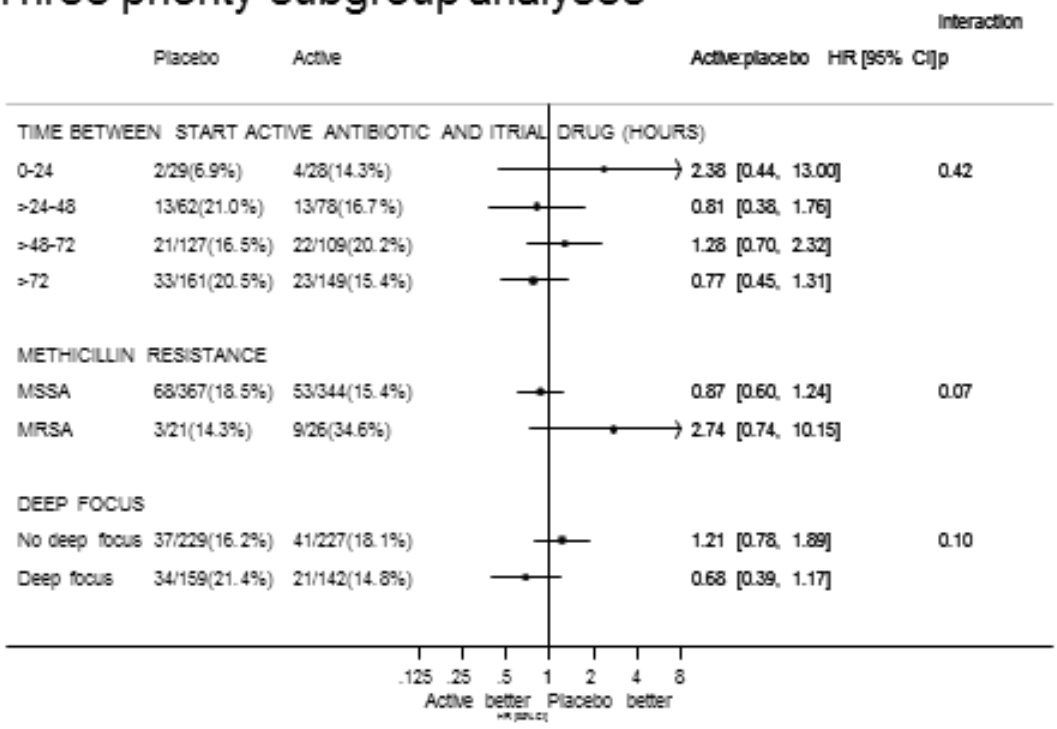


Figure 5 Bacteriological failure/recurrence or death (A) overall (B) according to three priority subgroups

Note: see **Figure 6** and **Figure 7** for other subgroup analyses.

Table 7 Failures, recurrences, deaths and ERC-adjudicated causes

	Bacteriological failure or recurrence			Clinical failure or recurrence			Deaths (all)	
	Placebo	Rifampicin	p	Placebo	Rifampicin	p	Placebo	Rifampicin
Total randomised	**388**	**370**	**-**	**388**	**370**	**-**	**388**	**370**
Total events	**71 (18.3%)**	**62 (16.8%)**	**0.81**	**86 (22.2%)**	**76 (20.5%)**	**0.84**	**56 (14.4%)**	**56 (15.1%)**
Failure	5 (1.3%)	4 (1.1%)	0.82	25 (6.4%)	23 (6.2%)	0.97		
Failure due to slow resolution	*3 (0.8%)*	*1 (0.3%)*		*17 (4.4%)*	*10 (2.7%)*			
Recurrence	16 (4.1%)	3 (0.8%)	0.01	23 (5.9%)	8 (2.2%)	0.01		
Death without either failure or recurrence	50 (12.9%)	55 (14.9%)	0.30	38 (9.8%)	45 (12.2%)	0.22		
Total failures/recurrences (first two columns) or *S. aureus* related deaths (third column): attributed by Endpoint Review Committee to:	**21 (100%)**	**7 (100%)**		**48 (100%)**	**31 (100%)**		**32 (100%)**	**36 (100%)**
Failure of antibiotics	1 (5%)	0		3 (6%)	1 (3%)		1 (3%)	3 (8%)
Failure of source management	17 (81%)	3 (43%)		38 (79%)	24 (77%)		21 (66%)	18 (50%)
Not recognised	*9 (43%)*	*2 (29%)*		*12 (25%)*	*5 (16%)*		*3 (9%)*	*4 (11%)*
Recognised, not actively managed	*5 (24%)*	*1 (14%)*		*16 (33%)*	*14 (45%)*		*8 (25%)*	*8 (22%)*
Recognised, actively managed still failed/recurred	*3 (14%)*	*0*		*10 (21%)*	*5 (16%)*		*10 (31%)*	*6 (17%)*
Not possible to distinguish	3 (14%)	4 (57%)		7 (15%)	6 (19%)		10 (31%)	15 (42%)
Death a consequence of late presentation	-	-		-	-		3 (9%)	11 (31%)

Subgroup analyses according to the three most important characteristics, time between starting active antibiotics and trial drug, methicillin resistance, and foci of infection (deep versus not deep), suggested no heterogeneity in lack of effect of rifampicin ($p_{heterogeneity}$ 0.42, 0.07, 0.10 respectively, **Figure 5B**. The rifampicin effect varied significantly according to the initial antibiotic given at randomisation, with some suggestion of benefit in those with methicillin-sensitive infection treated with flucloxacillin alone ($p_{heterogeneity}$=0.01, **Figure 6**), but across none of 16 other subgroup analyses ($p_{heterogeneity}$>0.05, **Figure 7**). At the suggestion of a reviewer we also considered subgroup analyses by diabetes ($p_{heterogeneity}$=0.37), weight ($p_{heterogeneity}$=0.13), BMI ($p_{heterogeneity}$=0.58) and dose in mg/kg ($p_{heterogeneity}$=0.42).

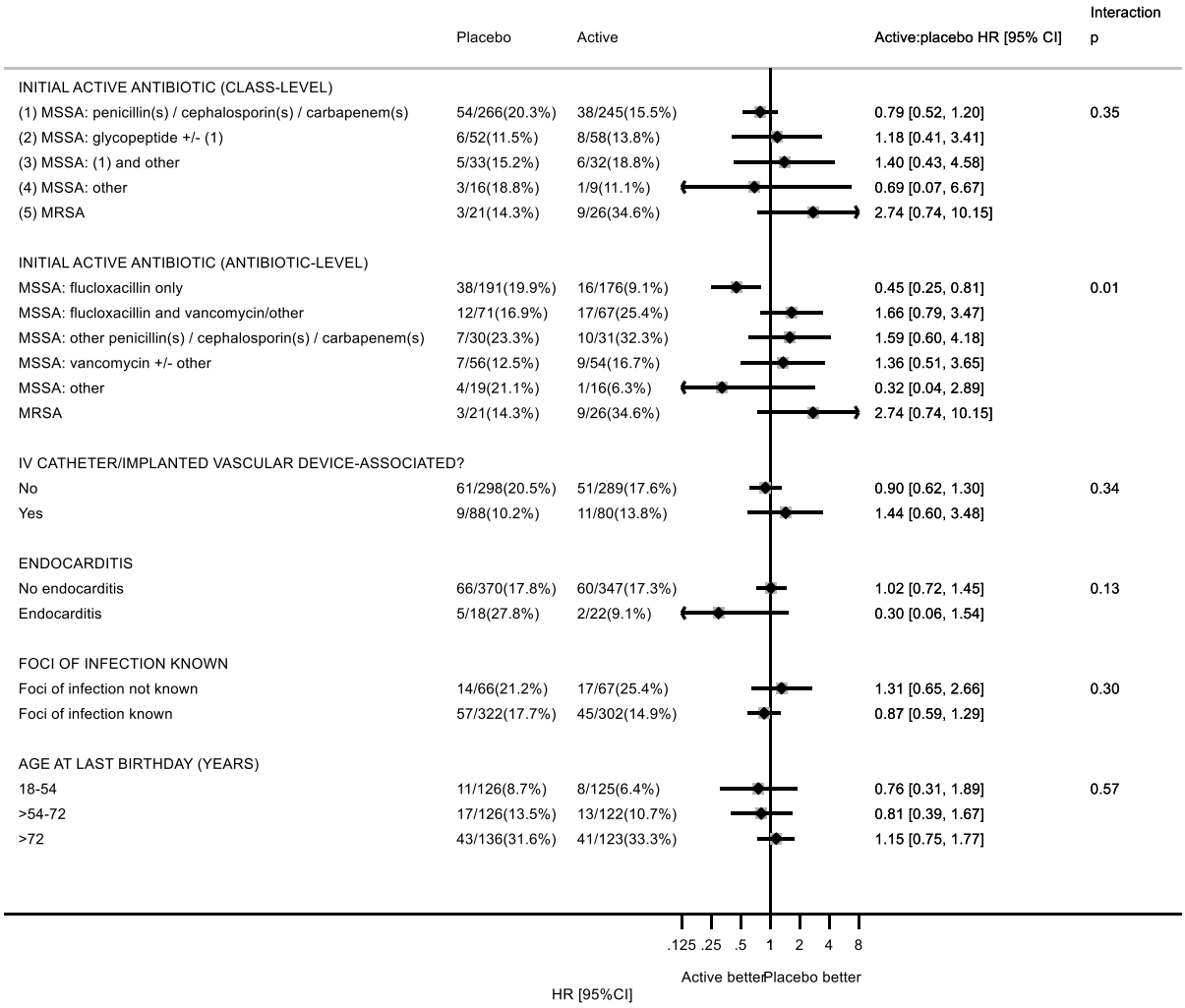
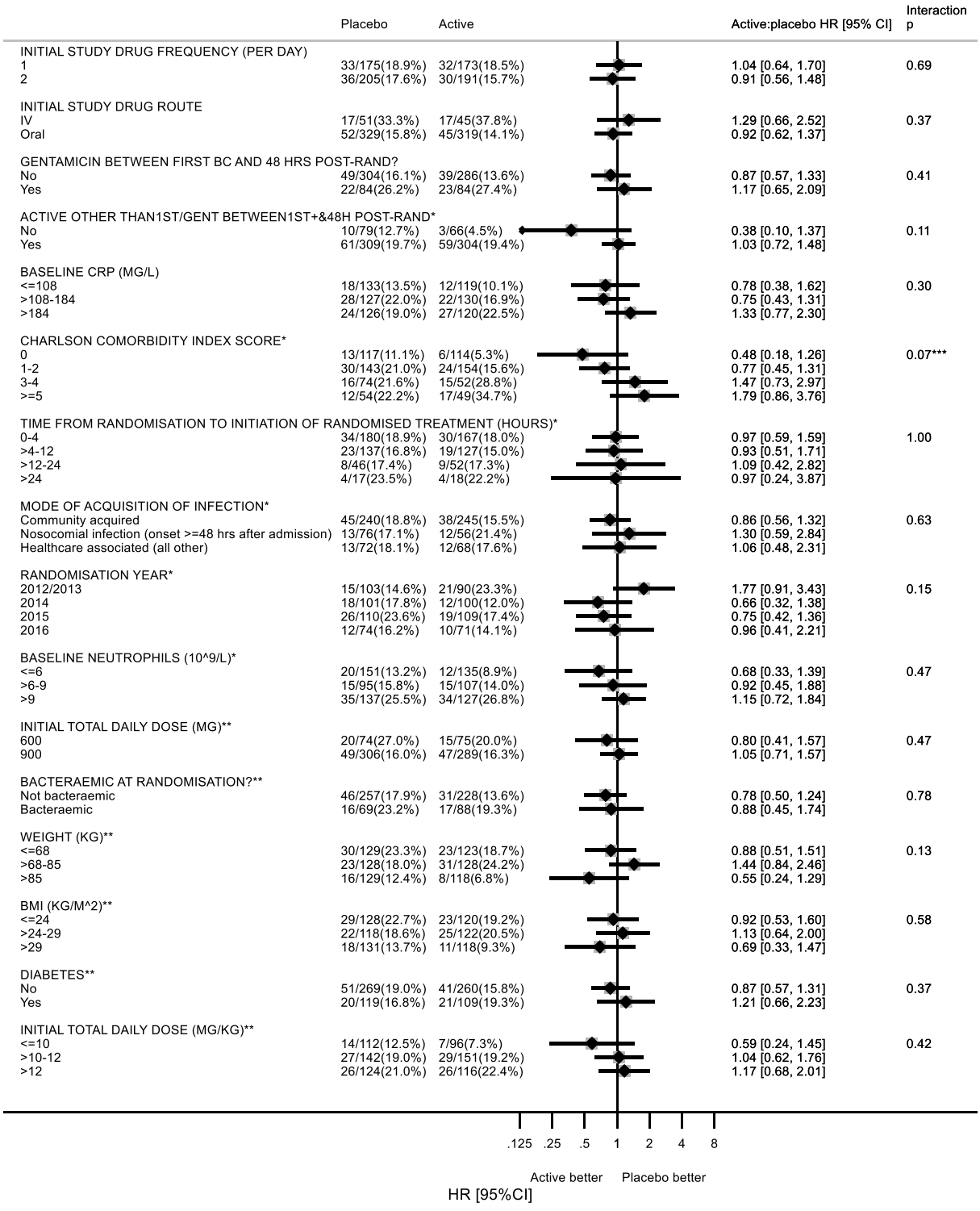


Figure 6 Five other priority subgroup analyses for bacteriological failure/recurrence or death through 12 weeks (primary endpoint)

Note: presenting class-level and antibiotic-level categorisation of initial active antibiotics (as per the Statistical Analysis Plan). See **Figure 5(b)** for the three other priority subgroup analyses defined in the Statistical Analysis Plan (time between starting active antibiotics and trial drug, methicillin resistance and foci of infection (deep versus not deep)). All eight priority subgroup analyses were pre-specified in the protocol and the Statistical Analysis Plan.



* subgroup analysis pre-specified in the statistical analysis plan but not the protocol
** additional subgroup analysis not in protocol or statistical analysis plan
*** p=0.07 using continuous interactions (splines); p=0.01 using continuous interaction (linear)

Figure 7 Twelve other subgroup analyses for bacteriological failure/recurrence or death through 12 weeks (primary endpoint)

Secondary endpoints

Clinically-defined failure/recurrence or death occurred in 76 (20.5%) rifampicin versus 86 (22.2%) placebo participants (RD=-1.4% (95% CI -7.4%,+4.7%); HR=0.97 (0.71-1.32) p=0.84, **Figure 8**). In exploratory post-hoc analyses, comparing rifampicin and placebo there were 23 (6.2%) versus 25 (6.4%) failures (competing-risks p=0.97), 8 (2.2%) versus 23 (5.9%) recurrences (competing-risks p=0.01), and 45 (12.2%) versus 38 (9.8%) deaths without clinically-defined failure/recurrence respectively (competing-risks p=0.22) (**Table 7**). The number-needed-to-treat to prevent one clinically-confirmed recurrence was 26.

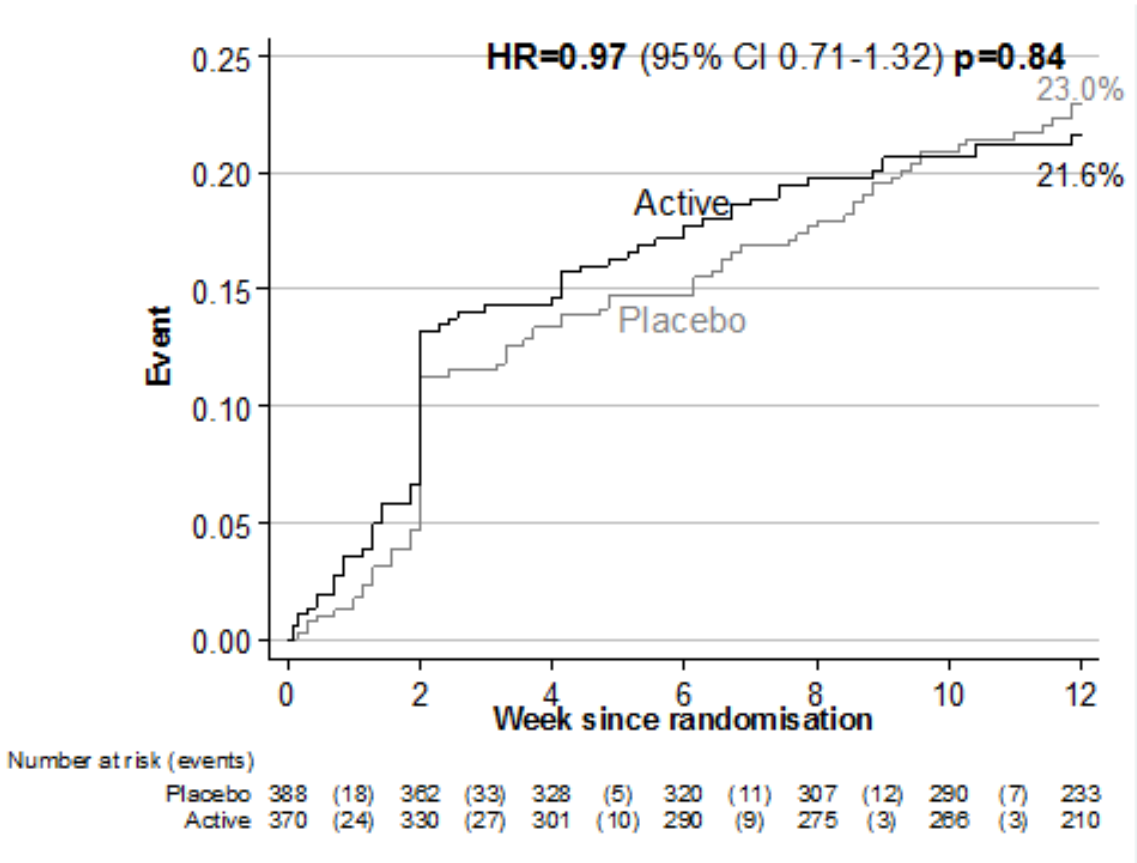


Figure 8 Clinically-defined failure/recurrence or death

The ERC adjudicated that failure of infection focus management was implicated in 38/48 (79%) on placebo versus 24/31 (77%) failures/recurrences on rifampicin (**Table 7**). Of these failures of infection focus management, there were 5 placebo versus 12 rifampicin participants where the focus was not recognized, 16 vs 14 respectively where the focus was recognised but not actively managed (e.g. because it was in an inaccessible site, or other

patient characteristics made intervention impossible) and 10 vs 5 respectively where the focus was recognised, actively managed, but despite this failure/recurrence still occurred. Failure of antibiotic therapy was implicated in the failure/recurrence in only 3 (6%) placebo vs 1 (3%) rifampicin failures/recurrences, with the cause being impossible to distinguish in the remaining 7 (15%) vs 6 (19%) respectively.

By 12-weeks, 56 (15.1%) rifampicin versus 56 (14.4%) placebo participants died (RD=+1.0% (95% CI -4.3%-6.2%); HR=1.10 (0.76-1.60) p=0.60, **Figure 9**). 25 (6.8%) rifampicin versus 17 (4.4%) placebo participants died before 2 weeks (HR=1.60 (0.86-2.95) p=0.13). 14 rifampicin versus 16 placebo deaths were adjudicated definitely *S. aureus*-related, 14 versus 12 probably *S. aureus*-related, and 8 versus 4 possibly *S. aureus*-related, respectively (**Table 27** in **Appendix 2**). 18 versus 23 were not attributed to *S. aureus* (remainder unattributable) (overall p=0.64).

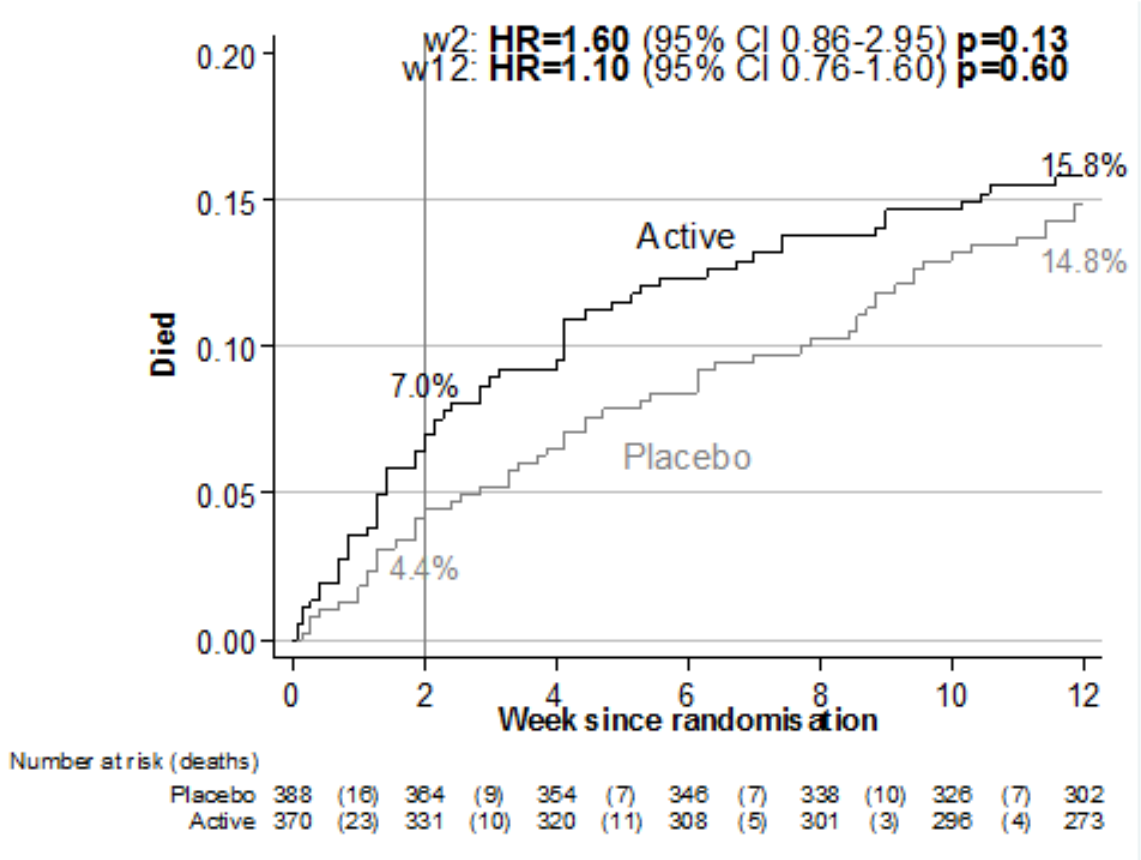


Figure 9 Mortality through 12 weeks

As for clinically-defined and bacteriologically-confirmed failures/recurrences, the ERC adjudicated that failure of infection focus management was implicated in most *S. aureus*-related deaths, 21/32 (66%) on placebo versus 18/36 (50%) on rifampicin (**Table 7**). Of these failures of infection focus management, there were 3 placebo versus 4 rifampicin participants where the focus was not recognized, 8 vs 8 respectively where the focus was recognised but not actively managed and 10 vs 6 respectively where the focus was recognised, actively managed, but despite this the participant still died from *S. aureus*. Failure of antibiotic therapy was implicated in only 1 (3%) placebo vs 3 (8%) rifampicin *S. aureus*-related deaths, with the relationship to antibiotics/focus management being impossible to distinguish in the remaining 10 (31%) vs 15 (42%) respectively. Three (9%) placebo versus 11 (31%) rifampicin *S. aureus*-related deaths were considered to have occurred as a consequence of late presentation to healthcare, i.e. were not preventable.

There was no difference in longer-term (post-week 12) survival between the groups, based on consented updates of vital status from routine electronic health records (p=0.69) (**Figure 10**).

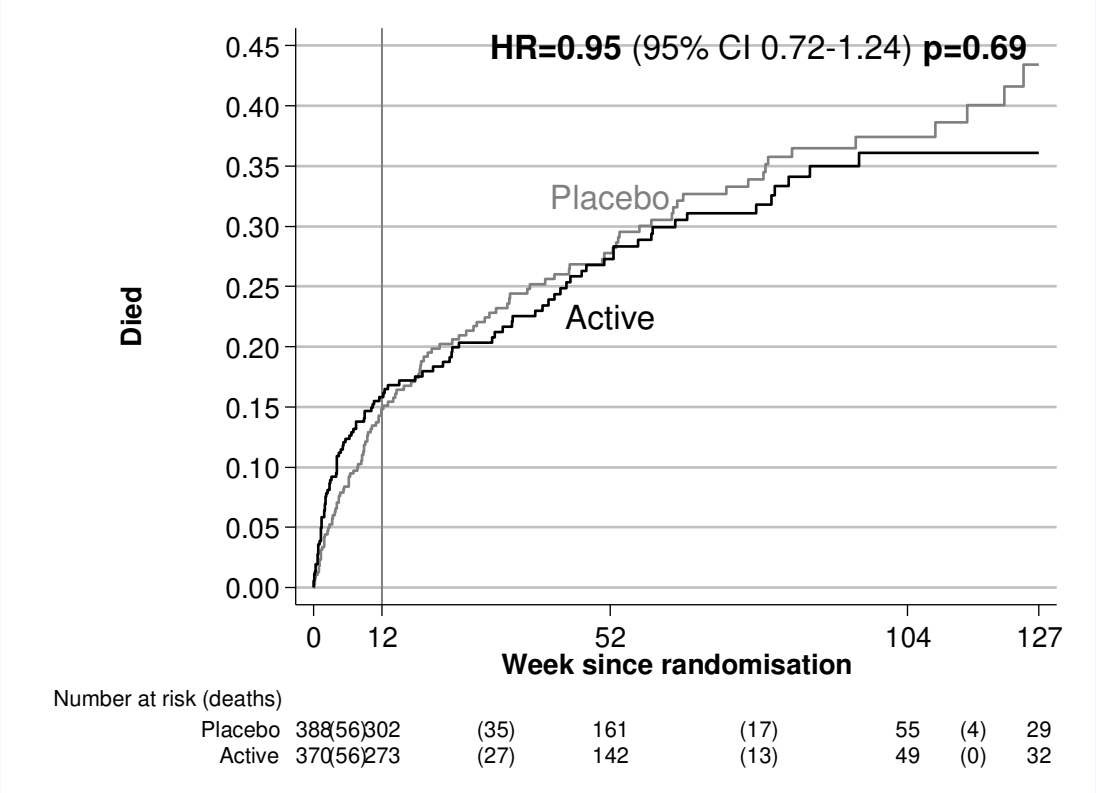


Figure 10 Mortality over the longer-term

Two (0.5%) rifampicin participants developed new rifampicin-resistant *S. aureus* bacteraemia 7 and 42 days after randomisation (p=0.24). One occurred on day 7 (followed by rifampicin discontinuation on day 11 and bacteriological failure on day 14); the other on day 42 (prescribed 14 days rifampicin; bacteriological recurrence on day 42). One additional participant had rifampicin-resistant *S. aureus* isolated from a permanent pacemaker wire removed on day 1 (within 4 hours of the first dose of trial drug). The screening blood culture had isolated a rifampicin-sensitive S. aureus. Further blood cultures were sterile for the remainder of follow-up. Following whole genome sequencing, the rifampicin resistant pacemaker isolate was 11 single nucleotide polymorphisms from the screening isolate and another isolate taken from the pacemaker on day-1, whereas these latter two isolates did not differ genetically, suggesting a diversity between isolates of more than 3 days in origin, and thus suggesting that the patient had a mixed infection with both rifampicin-resistant and rifampicin-susceptible strains that was not detected at screening.

There was no evidence that duration of bacteraemia was significantly shorter in those randomised to rifampicin (Figure 11; global p=0.66). Eighty-eight patients in the rifampicin group had positive blood cultures at enrolment. Of these 88, only one failed bacteriologically, none had bacteriological recurrence and none developed rifampicin-resistant infection. Eight failed clinically (including the one who failed bacteriologically) and two had clinical recurrence.

CRP declined significantly in both rifampicin and placebo groups, but decreases were smaller in rifampicin participants (global p=0.001, **Figure 11** Persistence of bacteraemia).

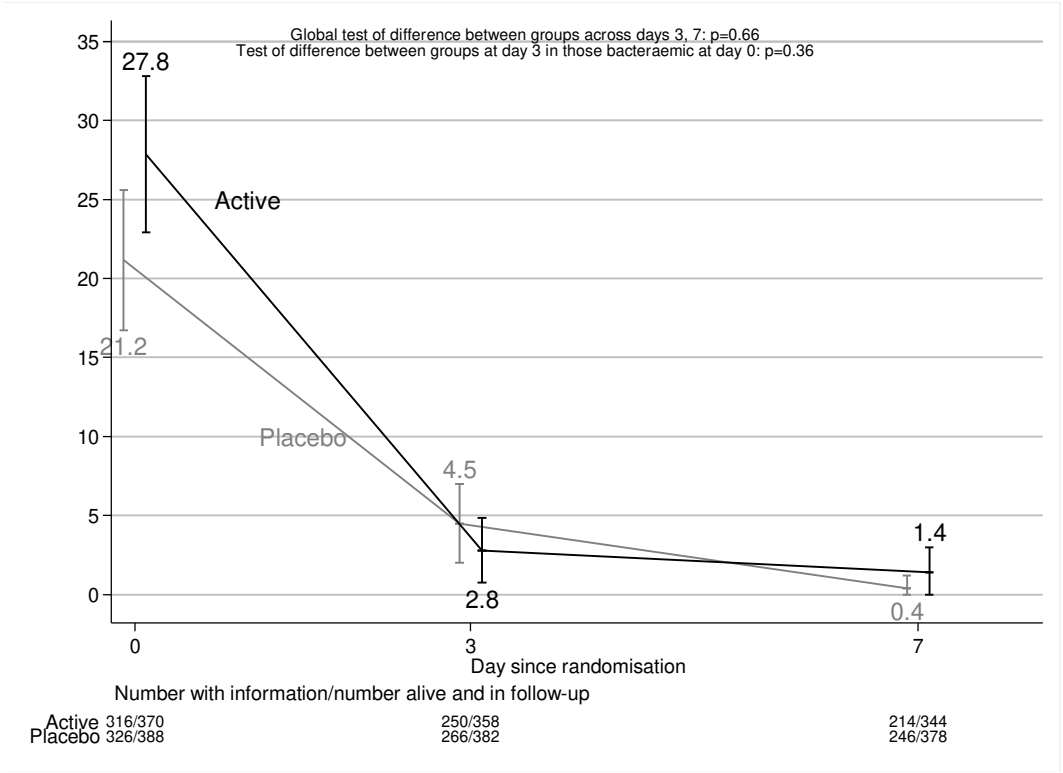


Figure 11 Persistence of bacteraemia

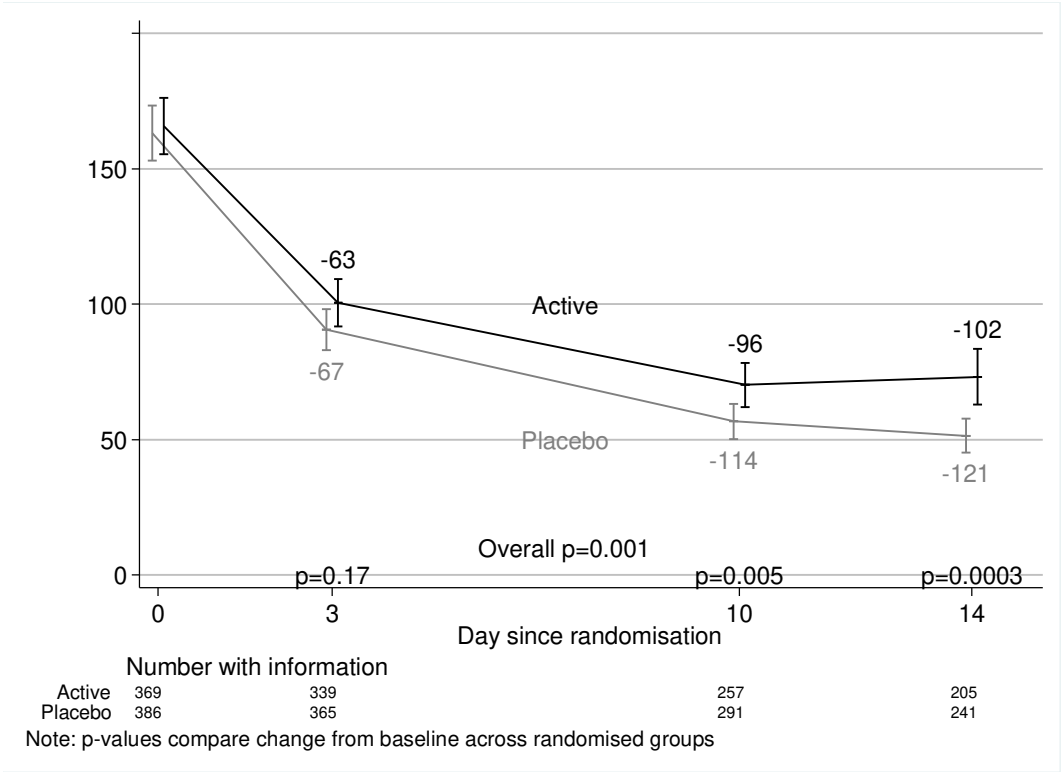


Figure 12 CRP over 2 weeks from randomisation

Safety

By 12-weeks, 101 (27.3%) rifampicin versus 94 (24.2%) placebo participants experienced 112 versus 116 SAEs (HR=1.21 (95% CI 0.92-1.61) p=0.17, **Figure 13**, **Table 8, Table 28** in **Appendix 2**). The most common type of SAE was related to Infections and infestations, the vast majority due to fatal events caused by *S. aureus* bacteraemia (non-fatal *S. aureus*-related adverse events were exempted from adverse event reporting in the protocol to avoid double counting disease failure/recurrence events).

Table 8 Summary of SAEs

SAEs	Placebo N=388	Rifampicin N=370	Total N=758	P
Any SAE	94 (24.2%) 116	101 (27.3%) 112	195 (25.7%) 228	0.36
Infections and infestations	39 (10.1%) 40	37 (10.0%) 38	76 (10.0%) 78	1.00
Cardiac disorders	13 (3.4%) 15	5 (1.4%) 6	18 (2.4%) 21	0.09
Vascular disorders	2 (0.5%) 2	4 (1.1%) 4	6 (0.8%) 6	0.44
Respiratory, thoracic and mediastinal disorders	12 (3.1%) 12	6 (1.6%) 6	18 (2.4%) 18	0.23
Gastrointestinal disorders	7 (1.8%) 7	10 (2.7%) 12	17 (2.2%) 19	0.47
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Renal and urinary disorders	4 (1.0%) 4	10 (2.7%) 10	14 (1.8%) 14	0.11
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	12 (3.1%) 12	11 (3.0%) 11	23 (3.0%) 23	1.00
Investigations	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Injury, poisoning and procedural complications	5 (1.3%) 5	3 (0.8%) 3	8 (1.1%) 8	0.73
Blood and lymphatic system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Metabolism and nutrition disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Psychiatric disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Nervous system disorders	5 (1.3%) 6	2 (0.5%) 2	7 (0.9%) 8	0.45

Note: Showing number of patients with one or more event (% of participants) number of events (e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)

Two rifampicin participants with pre-existing liver disease experienced non-fatal hepatic failure.

One 47-year old female required prolongation of hospitalisation for acute hepatic failure (grade 3) with raised INR (grade 2), ascites (grade 3) and acute renal failure (grade 3) which developed on ICU following 5 days rifampicin (900mg daily) with flucloxacillin. The participant had pre-existing Hepatitis C and chronic liver disease. Acute hepatic and renal failure was considered to have been triggered by sepsis. The participant recovered.

One 51-year-old female required prolongation of hospitalisation for decompensated liver disease (grade 3) with ascites (grade 3) following 14 days rifampicin (initially on 900 mg daily) with flucloxacillin. The participant did not mention liver disease at screening/enrolment and there was nothing in her medical notes regarding any past history of liver problems. When she developed decompensated liver disease with ascites, it was discovered that she had had a previous diagnosis of non-alcoholic steatosis (NASH) at another hospital several years previous, but was no longer under follow up. The participant recovered.

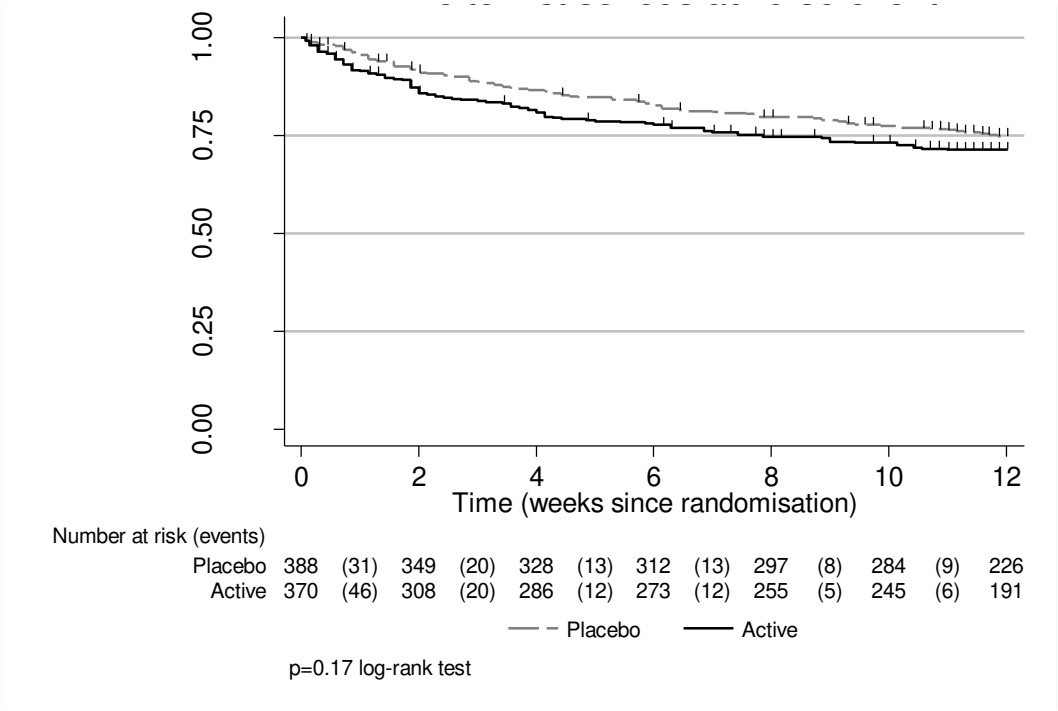


Figure 13 Time to first SAE

129 (34.9%) rifampicin versus 131 (33.8%) placebo participants experienced 209 versus 193 grade 3/4 AEs (HR=1.12 (95% CI 0.88-1.43) p=0.36, **Figure 14, Figure 14** Time to first grade 3 or 4 adverse event

Table 9**, Table 29** in **Appendix 2**). Most notable was a trend towards more renal grade 3/4 AEs with rifampicin which occurred in 19 (5.1%) versus 9 (2.3%) placebo participants (p=0.053); 17 versus 6 respectively being acute kidney injury.

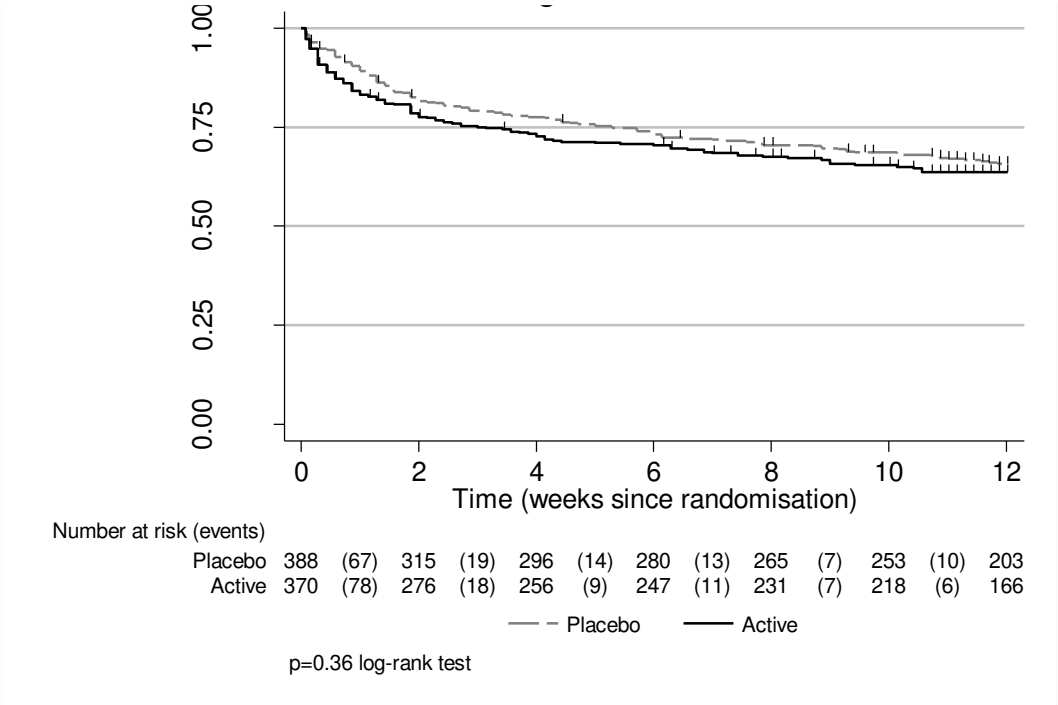


Figure 14 Time to first grade 3 or 4 adverse event

Table 9 Summary of Grade 3/4 adverse events

Grade 3/4 adverse events	Placebo N=388	Rifampicin N=370	Total N=758	P
Any grade 3/4 adverse event	131 (33.8%) 193	129 (34.9%) 209	260 (34.3%) 402	0.76
Infections and infestations	45 (11.6%) 53	40 (10.8%) 48	85 (11.2%) 101	0.82
Cardiac disorders	15 (3.9%) 17	6 (1.6%) 8	21 (2.8%) 25	0.08
Vascular disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Respiratory, thoracic and mediastinal disorders	16 (4.1%) 17	10 (2.7%) 11	26 (3.4%) 28	0.32
Gastrointestinal disorders	21 (5.4%) 24	29 (7.8%) 40	50 (6.6%) 64	0.19
Hepatobiliary disorders	0 (0.0%) 0	3 (0.8%) 3	3 (0.4%) 3	0.12
Skin and subcutaneous tissue disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Musculoskeletal and connective tissue disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Renal and urinary disorders	9 (2.3%) 9	19 (5.1%) 20	28 (3.7%) 29	0.053
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Reproductive system and breast disorders	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	11 (2.8%) 11	12 (3.2%) 12	23 (3.0%) 23	0.83
Investigations	6 (1.5%) 6	11 (3.0%) 16	17 (2.2%) 22	0.22
Injury, poisoning and procedural complications	6 (1.5%) 6	5 (1.4%) 5	11 (1.5%) 11	1.00
Surgical and medical procedures	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Blood and lymphatic system disorders	3 (0.8%) 3	5 (1.4%) 6	8 (1.1%) 9	0.50
Metabolism and nutrition disorders	3 (0.8%) 3	5 (1.4%) 6	8 (1.1%) 9	0.50
Psychiatric disorders	5 (1.3%) 5	5 (1.4%) 6	10 (1.3%) 11	1.00
Nervous system disorders	11 (2.8%) 14	4 (1.1%) 4	15 (2.0%) 18	0.12
Eye disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00

Note: Showing number of patients with one or more event (% of participants) number of events (e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)

63 (17.0%) rifampicin versus 39 (10.1%) placebo experienced 89 versus 52 antibiotic-modifying AEs (sub-distribution HR=1.78 (1.20-2.65) p=0.004; **Figure 15**, **Figure 15** Time to first antibiotic-modifying adverse event

Table 10, **Table 30** in **Appendix 2**). Gastrointestinal disorders (24 versus 8 participants, respectively, p=0.003) and renal/urinary disorders (8 versus 1 participants, respectively, p=0.02) were more common with rifampicin, as were events classified as general disorders and administration site conditions (13 vs 4 participants), which included some drug interactions (see below).

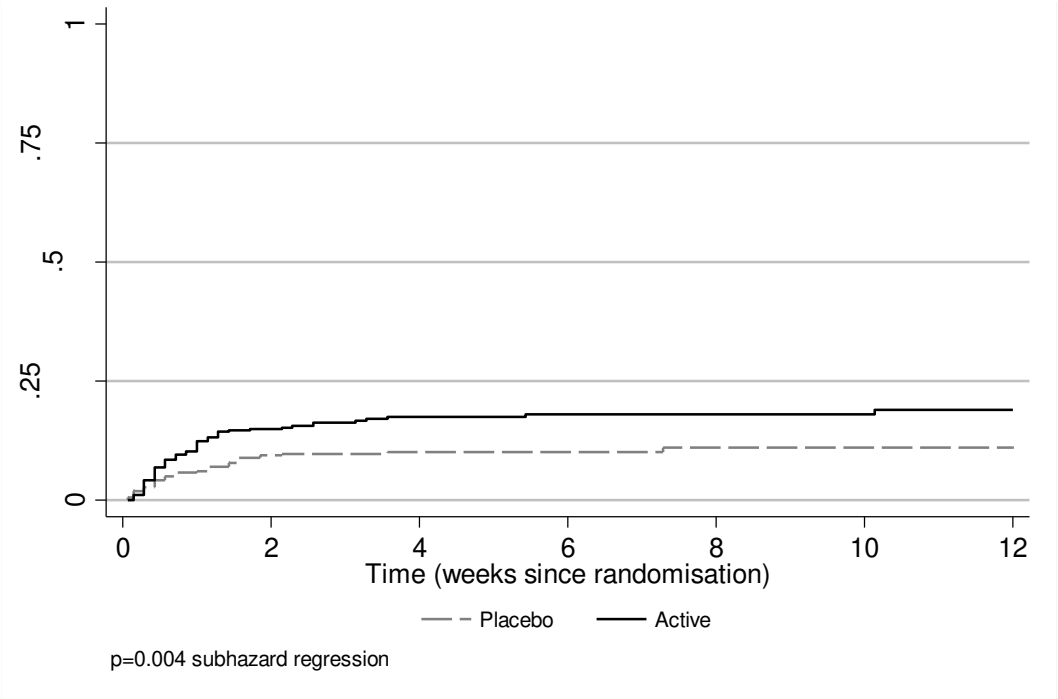


Figure 15 Time to first antibiotic-modifying adverse event

Table 10 Summary of antibiotic-modifying adverse events

Antibiotic-modifying adverse events	Placebo N=388	Rifampicin N=370	Total N=758	P
Any antibiotic-modifying adverse event	39 (10.1%) 52	63 (17.0%) 89	102 (13.5%) 141	0.006
Infections and infestations	3 (0.8%) 3	5 (1.4%) 5	8 (1.1%) 8	0.50
Respiratory, thoracic and mediastinal disorders	2 (0.5%) 4	0 (0.0%) 0	2 (0.3%) 4	0.50
Gastrointestinal disorders	8 (2.1%) 9	24 (6.5%) 32	32 (4.2%) 41	0.003
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	7 (1.8%) 9	8 (2.2%) 9	15 (2.0%) 18	0.80
Renal and urinary disorders	1 (0.3%) 2	8 (2.2%) 10	9 (1.2%) 12	0.02
General disorders and administration site conditions	4 (1.0%) 4	13 (3.5%) 13	17 (2.2%) 17	0.03
Investigations	12 (3.1%) 13	12 (3.2%) 14	24 (3.2%) 27	1.00
Injury, poisoning and procedural complications	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
Blood and lymphatic system disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Metabolism and nutrition disorders	2 (0.5%) 3	0 (0.0%) 0	2 (0.3%) 3	0.50

Antibiotic-modifying adverse events	Placebo N=388	Rifampicin N=370	Total N=758	P
Psychiatric disorders	1 (0.3%) 2	0 (0.0%) 0	1 (0.1%) 2	1.00
Nervous system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00

Note: Showing number of patients with one or more event (% of participants) number of events
(e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)

24 (6.5%) rifampicin versus 6 (1.5%) placebo experienced drug-interactions with antibiotics or other drugs (p=0.0005); 13 versus 4 led to discontinuation of trial drug (p=0.03), 14 versus 3 respectively led to grade 1/2 AEs (p=0.006), and 5 versus 2 respectively to grade 3/4 AEs (p=0.27).

There was no evidence of differences between groups in changes in ALT (global p=0.18, **Figure 16**) or alkaline phosphatase (global p=0.11, **Figure** 16 ALT over 2 weeks from randomisation

). Bilirubin increased significantly in the rifampicin group at day-3 (p<0.0001; global p<0.0001; **Figure 17** Alkaline phosphatase over 2 weeks from randomisation

). Very few participants experienced grade 3 or 4 elevations in these laboratory parameters (**Table 11**).

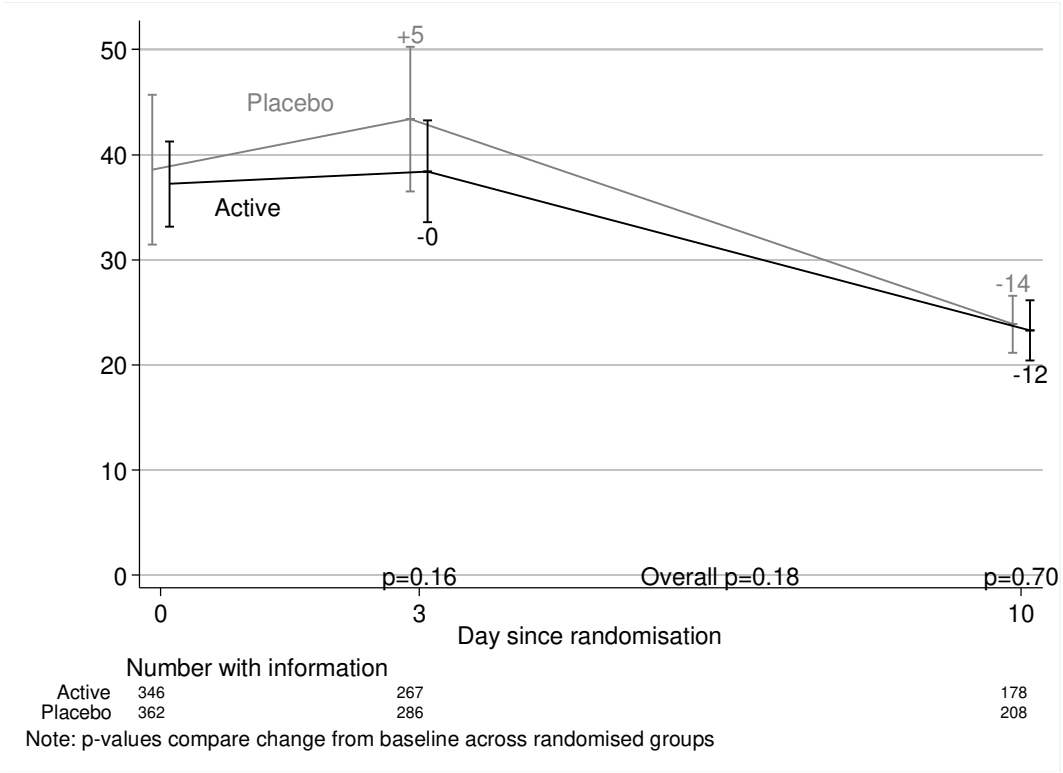


Figure 16 ALT over 2 weeks from randomisation

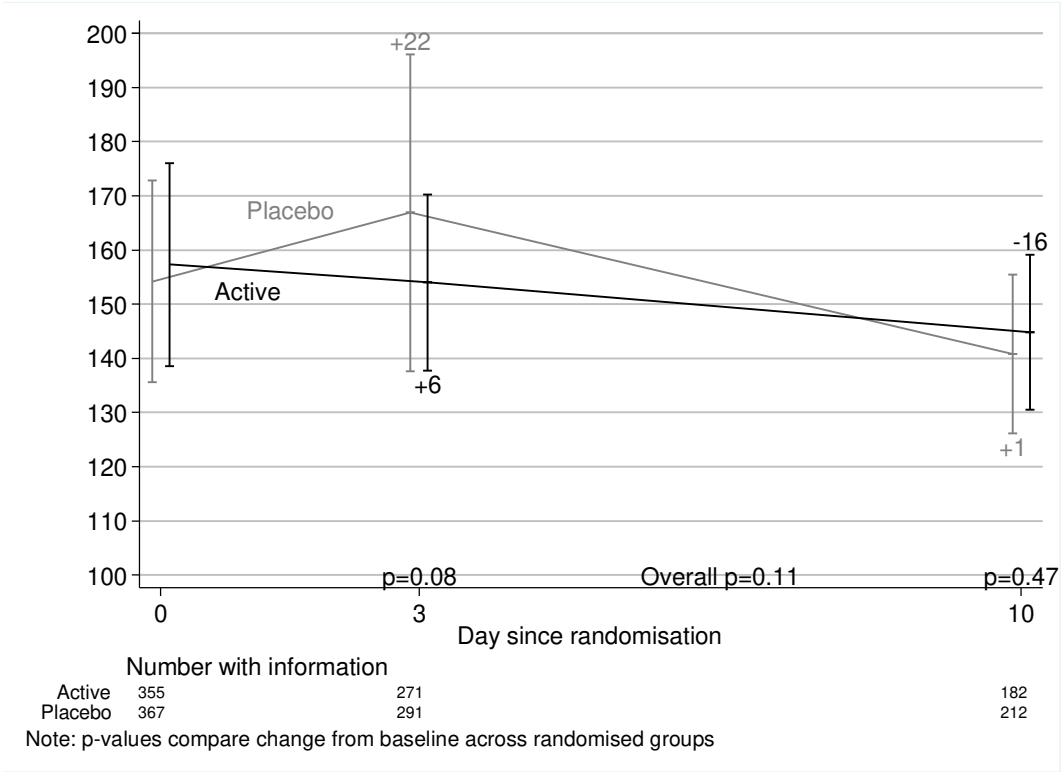


Figure 17 Alkaline phosphatase over 2 weeks from randomisation

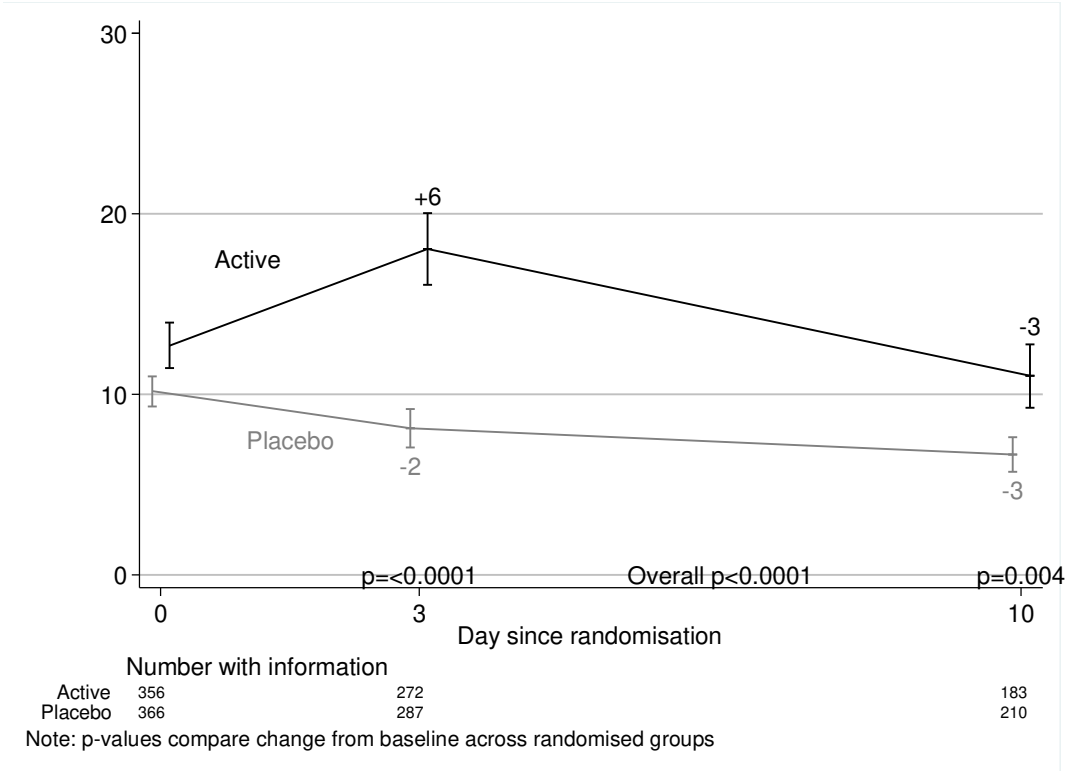


Figure 18 Bilirubin over 2 weeks from randomisation

Table 11 Graded toxicity in ALT, alkaline phosphatase and bilirubin

	Placebo	Active	Total
ALT - Day 0			
Normal	274 (74.5%)	268 (75.1%)	542 (74.8%)
>ULN - 3.0 x ULN (grade 1)	85 (23.1%)	81 (22.7%)	166 (22.9%)
>3.0 - 5.0 x ULN (grade 2)	6 (1.6%)	5 (1.4%)	11 (1.5%)
>5.0 - 20.0 x ULN (grade 3)	2 (0.5%)	3 (0.8%)	5 (0.7%)
>20.0 x ULN (grade 4)	1 (0.3%)	0 (0.0%)	1 (0.1%)
ALT - Day 3			
Normal	202 (70.6%)	203 (76.0%)	405 (73.2%)
>ULN - 3.0 x ULN (grade 1)	70 (24.5%)	50 (18.7%)	120 (21.7%)
>3.0 - 5.0 x ULN (grade 2)	8 (2.8%)	12 (4.5%)	20 (3.6%)
>5.0 - 20.0 x ULN (grade 3)	6 (2.1%)	2 (0.7%)	8 (1.4%)
ALT - Day 10			
Normal	182 (87.5%)	160 (89.9%)	342 (88.6%)
>ULN - 3.0 x ULN (grade 1)	24 (11.5%)	17 (9.6%)	41 (10.6%)
>3.0 - 5.0 x ULN (grade 2)	2 (1.0%)	1 (0.6%)	3 (0.8%)
Alkaline phosphatase - Day 0			
Normal	267 (71.8%)	252 (69.2%)	519 (70.5%)
>ULN - 2.5 x ULN (grade 1)	90 (24.2%)	101 (27.7%)	191 (26.0%)
>2.5 - 5.0 x ULN (grade 2)	13 (3.5%)	9 (2.5%)	22 (3.0%)
>5.0 - 20.0 x ULN (grade 3)	2 (0.5%)	2 (0.5%)	4 (0.5%)
Alkaline phosphatase - Day 3			
Normal	196 (67.4%)	175 (64.6%)	371 (66.0%)
>ULN - 2.5 x ULN (grade 1)	82 (28.2%)	91 (33.6%)	173 (30.8%)
>2.5 - 5.0 x ULN (grade 2)	11 (3.8%)	2 (0.7%)	13 (2.3%)
>5.0 - 20.0 x ULN (grade 3)	1 (0.3%)	3 (1.1%)	4 (0.7%)
>20.0 x ULN (grade 4)	1 (0.3%)	0 (0.0%)	1 (0.2%)
Alkaline phosphatase - Day 10			
Normal	149 (70.3%)	119 (65.4%)	268 (68.0%)
>ULN - 2.5 x ULN (grade 1)	57 (26.9%)	58 (31.9%)	115 (29.2%)
>2.5 - 5.0 x ULN (grade 2)	6 (2.8%)	5 (2.7%)	11 (2.8%)
Bilirubin - Day 0			
Normal	341 (91.7%)	309 (85.1%)	650 (88.4%)
>ULN - 1.5 x ULN (grade 1)	14 (3.8%)	31 (8.5%)	45 (6.1%)
>1.5 - 3.0 x ULN (grade 2)	17 (4.6%)	17 (4.7%)	34 (4.6%)
>3.0 - 10.0 x ULN (grade 3)	0 (0.0%)	6 (1.7%)	6 (0.8%)
Bilirubin - Day 3			
Normal	270 (94.1%)	190 (69.9%)	460 (82.3%)
>ULN - 1.5 x ULN (grade 1)	11 (3.8%)	35 (12.9%)	46 (8.2%)
>1.5 - 3.0 x ULN (grade 2)	3 (1.0%)	35 (12.9%)	38 (6.8%)
>3.0 - 10.0 x ULN (grade 3)	3 (1.0%)	12 (4.4%)	15 (2.7%)
Bilirubin - Day 10			
Normal	200 (95.2%)	162 (88.5%)	362 (92.1%)
>ULN - 1.5 x ULN (grade 1)	6 (2.9%)	7 (3.8%)	13 (3.3%)
>1.5 - 3.0 x ULN (grade 2)	4 (1.9%)	12 (6.6%)	16 (4.1%)
>3.0 - 10.0 x ULN (grade 3)	0 (0.0%)	2 (1.1%)	2 (0.5%)

Chapter 4 Trial Participation Qualitative Sub-study

(Note: this chapter includes material that has been adapted from the trial protocol which has been published in Trials 2012 13:241.)

Experiences of being approached for trial participation, the consenting process and trial participation

The overall objective of this sub-study was to identify patient and personal legal representative barriers to recruitment. The study was led by Jennifer Bostock, the trial PPI representative. The sub study had two components: the first involved patients/legal representatives who **did not** consent to trial recruitment, and the second involved patients/legal representatives who **did** consent to trial recruitment.

Patient/legal representatives who did not consent to trial recruitment

The overall objective of this sub-study was to identify patient and legal representative barriers to recruitment, in order:

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.

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 were given a short, completely anonymous, questionnaire with a freepost envelope, which could be completed at any time in the future and posted directly to the MRC Clinical Trials Unit at UCL. 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 were also be provided with a parallel questionnaire.

At the Guy's and St Thomas' centre, at the end of the questionnaire, participants/legal representatives were offered the option of being interviewed by the ARREST PPI advisor. If they agreed to be interviewed, they were asked to provide their name and contact details, and this would indicate consent for an interview. The aim was to get experiences from ~3 participants and ~3 personal 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 followed the questions in the questionnaire, seeking to obtain a more complete narrative of experiences around each aspect.

Patient/legal representatives who did consent to trial recruitment

The overall objective was to sample views on experiences of trial participation: to assess what participants or their (personal) legal representatives liked, and what they did not like and think could have been done better. This was in order:

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 (at the time) 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 were 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 was an interview study conducted at one centre, Guy's and St Thomas' NHS Trust. Since participants were typically very unwell when they joined the study, the approach to each patient to discuss the interview study and seek additional consent was made at a varying time after randomisation depending on clinical status. For most patients this was between 2-3

weeks from randomisation, when their clinical status had improved and discharge was being planned. However, it could have been at any time up to their final 12 week ARREST follow-up visit. The research nurse provided an additional information sheet 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 agreed and provided consent for this additional interview, then the ARREST PPI advisor conducted the interview on the telephone at a time that was convenient for the participant. Participants who gave consent originally or subsequently and legal representatives who gave consent for relative/friend participation were approached.

The aim was to get experiences from ~3 participants and ~3 personal legal representatives (who were 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 was semi-structured. The first set of questions explored 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?

The second set of questions explored 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 (i.e. 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).

Findings

The study revealed two findings: firstly there was a disappointing uptake of both questionnaire completion and interview. 20 questionnaires were sent and only 7 responded and 3 patients/legal representatives were interviewed. Whilst it was expected that the study would be challenging and unorthodox in such a trial (especially seeking to explore views of those who did not consent), it was not anticipated that uptake would be as low as it was.

For patients who **did not** consent, the reasons given were:

'*Everything else going on was too much*', *'could not make a decision either way', 'best to play safe', 'felt too ill/tired', 'did not have enough time to decide'*. Another added, *"would have liked to take part but the side effects were too risky & I didn't want to take any risks. Everything was explained really well, sorry I couldn't help*". The same patient said that, *'more time to decide'* was very important and would have improved the likelihood of him participating. Another patient who gave similar reasons said that s/he would have been more likely to have participated if the, *'information sheet was shorter'*.

One questionnaire was sent back without any questions being answered but with a narrative arguing that it was not appropriate for patients who were, *"very unwell in A&E. to be hassled by a research nurse about studies that are going on"*. The patient went on to state, *"I fully understand and appreciate trials take place and have taken part in clinical trials. Timing is the key & explaining when people feel a bit more human and can think straight about partaking when they have had time to read & digest it*." Whilst this was only one patient it is

important that all studies seeking to recruit those with serious illness do so in a manner which is sensitive to the needs of patients. The fact that only one patient used the questionnaire or interview as an opportunity to complain in this way is evidence of the careful and considerate method of recruitment displayed by the recruiting staff.

Reasons given by personal legal representatives why they did NOT want their relative to participate were:

'Felt too worried', too much responsibility', 'worried that my relative might ***GET*** *the study drug' = 'worried about side effects and liver problems'.*

For patients who **did** consent, the reasons given were:

"I didn't really need time to think about it, I was ill and so it's all rather difficult" & *"I don't remember what the information sheet was like but Karen explained it all to me and I don't think I had any questions, but I'm sure she would have answered them if I had some".* Another said, *"It's not about the information, I just thought well I've got nothing to lose, but I did ask them to come back the next day and I thought about it, asked some people and still came to the same conclusion that I had nothing to lose so the next day I just signed up".*

The reasons given by personal legal representatives why they consented to their relative participating were:

"To help my mum and perhaps other people, it's a 50/50 chance of her getting the medicine or the placebo and I just thought she might be helped". On the information given they said, *"But to be honest I don't think I even read that sheet. Well I suppose the stuff about safety they told me about and I read it, it wasn't difficult to understand. I just signed it and they were helpful the people who told me about it".*

What have we learned?

Despite the limited responses it is possible to draw some lessons for the future from this small study. These are:

1. Some things researchers cannot change but others they can. The *'felt too ill/tired & 'had too much going on"* might be decreased if researchers delayed recruitment until the patients feel a little better (although this was not be possible in the present trial given the requirement for <96 hours of treatment).
2. Similarly *'not enough time to decide'* is something that can be changed, *'Information sheet too long'* can also be altered.
3. More subtle and challenging adaptations might come when consideration is given to comments such as, *'worried that my relative might GET the study drug'*. Whilst honesty is paramount, promoting the reason for the trial and the reason why this medicine is being studied might help sway the balance in favour of the risk being worth taking.

CONCLUSION

It is unusual for a trial such as this to explore these issues and it is challenging ethically to gain approval to conduct a study approaching patients/representatives who did not consent to participate in the primary study. However it was deemed important both by the trial team for this and future research, and by our PPI advisor for the benefit of patients and their representatives. Having gained ethical approval for this study and having learned lessons on how to improve in future we are confident that other research will benefit from the lessons, methods and findings of this small study. A number of practical suggestions were made based upon the findings and were presented at an Investigator meeting by the PPI advisor. It is hoped that these suggestions and the model for this sub study will be used by those at the meeting and their wider research networks.

Chapter 5 Economic and Health-Related Quality of life consequences of *S. aureus* bacteraemia, and effect of treatment with adjunctive rifampicin

Introduction

The ARREST trial was designed to evaluate the efficacy of adjunctive rifampicin in reducing bacteriologically-confirmed failure or recurrence of *S. aureus* bacteraemia or death in 12 weeks. The trial did not provide evidence that rifampicin improves the composite primary endpoint. However, analyses of the components of this composite primary endpoint suggested that adjunctive rifampicin reduced the risk of disease recurrence. Nevertheless, the trial did not find any impact of rifampicin on short- or longer-term mortality (secondary outcomes). Rifampicin also significantly complicated other drug treatment. Hence, clinically, adjunctive rifampicin was not considered to provide overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

The trial's pragmatic design means the population included is clinically relevant, and non-comparative findings can be considered generalisable. The clinical results highlight the severity of *S. aureus* bacteraemia and also show the high degree of heterogeneity in the patient population. In this component of the analyses, we firstly describe the trial evidence on the Health Related Quality of Life (throughout abbreviated to HRQoL) and economic consequences of an *S. aureus* bacteraemia episode in this patient population – which can inform the burden to patients (in terms of HRQoL) and to health systems (in terms of health system costs). We also explore heterogeneity by evaluating determinants of costs and HRQoL. Quantifying the burden of *S. aureus* bacteraemia allows better informed future evaluations of alternative treatment and prevention strategies, a research area which has been highlighted.[35] Whilst the literature on the economic impact of *S. aureus* bacteraemia is substantial, particularly for methicillin-resistant strains (MRSA), the evidence it is based on is poor and often does not rely on any empirical data.[36]

Whilst evaluation of the costs and HRQoL impacts of *S. aureus* bacteraemia, and potential determinants of these, are the main focus of our analyses, given the trial's primary aim we will also investigate the effect of adjunctive rifampicin on HRQoL and cost outcomes. From the results of the clinical analyses it can be hypothesised that rifampicin adjunctive treatment may be associated with cost savings and improvements in HRQoL via the small but significant reduction in bacteriologically and clinically-defined disease recurrences

(hypothesised to arise from the sterilisation of deep infection foci). The trial data will be used to determine the potential cost-effectiveness of adjunctive rifampicin treatment, and given the likely high degree of uncertainty, the value of further research will be determined.

Methods

Cost and health outcomes for patients with *S. aureus* bacteraemia were evaluated using data from the ARREST trial. Health outcomes were measured as quality-adjusted life years (QALYs). The QALY combines survival and health-related quality of life (HRQoL) into a single metric, where time spent with poorer HRQoL is downweighted. Costs considered in analysis were those incurred by the NHS and Personal Social Services (PSS), as recommended by the National Institute for Health and Care Excellence (NICE).[37] Costs and QALYs were measured only for 84 days (i.e. 12 weeks) from the date of randomisation, which was also the maximum duration of active follow-up (longer follow-up through electronic health records was done only for mortality). When considering determinants of costs and QALYs, the effect of adjunctive rifampicin was evaluated, which allowed for a cost-effectiveness analysis to be conducted. Given the short time horizon, neither costs nor health benefits were discounted. The analysis was conducted using the statistical software R version 3.4.1.[38]

Details of each component of analyses (analyses of health benefits; analysis of costs; and analysis of cost-effectiveness and value of information) are presented below. This is followed by a description of the statistical methods used.

Costs

Data on the use of *S. aureus* bacteraemia-related healthcare resources was collected during the trial and served as the basis for the calculation of total costs included in this analysis. Data related to three different resource use categories:

a) All antibiotic therapy received from randomisation in the active follow-up period (84 days), including trial drug and any other antibiotic therapy used;
b) First admissions and re-admissions to secondary care and length of stay, including investigations and procedures undertaken while hospitalised;
c) Consultations with healthcare providers (in primary or secondary care) after hospital discharge from first hospital admission.

See **Appendix 3** for the resource use questions on the electronic case record forms. Costs for each trial participant were calculated as the product of health resources used during the trial follow-up period and the relevant NHS unit costs. Unit costs were based on the NHS Reference Cost (NHS-RF) data for 2013/14[39] and 2015/16,[40] the Unit Costs of Health and Social Care 2016 (PSSRU),[41] the British National Formulary (BNF),[42] and relevant literature. All values are in British pound sterling (£) and were, where required, updated to 2016 prices.[hospital and community health services (HCHS) index provided by the PSSRU 2016]

Antibiotic therapy

Antibiotic regimens used during the trial were costed using information on the agent, dose, frequency and route of administration. For rifampicin this information was recorded in trial drug logs by healthcare professionals until the earlier of 14 days or cessation of 'backbone' antibiotics. Time (in days) from initiation to end of randomised treatment was estimated and used to estimate the overall on trial drug cost per patient during follow-up period. The use of other antibiotics was recorded by healthcare professionals in treatment logs completed at each change in therapy until end of follow-up or death. Time (in days) on other antibiotics was also estimated and was mainly informed by administration 'start' and 'stop' information. Only antibiotics taken after randomisation were considered. As for the trial drug, estimated time (in days) on other antibiotics only considered time from randomisation.

Table 31A in **Appendix 2** lists, for all antibiotic therapies costed in the trial, including the trial drug, the unit costs by dose and route of administration. **Table 31B** lists antibiotic therapies by dose and route for which a unit cost was not obtained.

Admissions to secondary care

With regards to hospital inpatient stay, health resource utilisation was recorded by study personnel at weekly clinical assessments until discharge, and then at the final day 84 follow-up visit. These include days spent in wards, including Intensive Care (ITU), or High Dependency Units (HDU), or investigations and procedures (e.g. computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, PET (positron emission tomography scan). Haematology and biochemistry test results were only collected at specific time points, thus were not included. The use of other drugs and the consequences of drug-drug interactions or adverse events were not collected. Hospital readmission information provided at the final day-84 visit was also considered; this included readmission as hospital day cases, readmissions with hospital stay to hospital ward, ITU or HDU, together with all procedures undertaken

after re-hospitalisation. As trial patients were expected to have a long stay in hospital in their initial hospitalisation (i.e. number of days from admission to hospital to first post-enrolment discharge), unit costs from non-elective long stay tariffs were used. This analysis used only days in hospital after randomisation (in contrast with chapter 3 that looked at duration of the entire admission). The unit costs used to calculate the cost of secondary-care-related health consumption in the trial are summarised in **Table 32** in **Appendix 2**.

Consultations with healthcare providers

Data on the number of consultations with healthcare providers were available for discharged patients from participant-reported questionnaires at the final 84-day follow-up. For the period since discharge, each trial participant recorded the number of GP consultations (either at doctor's surgery or at home) and number of hospital outpatient visits with a doctor or nurse, separating the number of those that were *S. aureus* bacteraemia-related from those that were not. All health consultations reported were included in the economic analysis. The unit costs used to cost these are again summarised in **Table 32** in **Appendix 2**.

Health-related quality of life

The health outcome used was total QALYs over 84 days (i.e. period of active follow-up). Data on the EQ-5D-3L instrument, a widely recognised and validated HRQoL descriptive system,[43,44] was collected at baseline and at 7, 14 and 84 days. The recent five-response version of the EQ-5D, the EQ-5D-5L, and associated UK-specific valuation set were not fully available at the start of this study.

The EQ-5D-3L questionnaire has five questions, each relating to a different health dimension: mobility, self-care, ability to undertake usual activity, pain and anxiety/depression. Each question allows three possible responses: no problems, moderate problems and severe problems. Based on their answers, participants can hence be classified as 1 of 243 possible health states *plus* death and unconscious health states. A separate algorithm was then applied to identify the impact of the particular health state on HRQoL, i.e. a weight, where full health assumes a value of 1, death a value of zero, and where values below zero represent health states worse than death. The algorithm used to generate the weights was based on a population study that elicited societal preferences using a time trade-off technique (a technique that, for instance, asks participants how many years in the current health state they would be willing to 'trade off' for a shorter period in full health).[45,46]

In this study, QALYs were estimated using the area under the curve method with interpolation of EQ-5D-3L index scores measured at the beginning and end of each time interval. Hence, for each study participant, and when sufficient data available, a QALY estimate was obtained considering the product of the mean EQ-5D-3L index score during the interval and the duration of the interval.[49]

Statistical methods of analyses

Missingness

Given that the population recruited into the trial contain a proportion of critically ill patients, we expected non-negligible missingness on the EQ-5D data. It is typical of trials in very sick participants, such as ARREST, to recruit or have during the follow-up period, a non-negligible proportion of individuals in a coma. To these patients (n=80 (10.6%) at baseline; n=48 at 7 days; n=38 at 14 days; and n=4 at 84 days) a HRQoL weight of -0.402 was assigned.(48, 49) Some patients were also reported to be unable/unwilling to provide EQ-5D answers (n=20 (2.6%) at baseline; n=18 at 7 days; n=12 at 14 days; and n=10 at 84 days). These patients were assumed to have a HRQoL weight value of -0.261, corresponding to the bottom decile of the EQ-5D index score distribution of all trial patients for which a EQ-5D index score was available. As a sensitivity analysis EQ-5D answers for unable/unwilling patients were kept missing.

In the estimation of QALYs over the 84-day period, interpolation between adjacent assessments was used. Where EQ-5D information was missing at 7 and/or 14 days interpolation used the other (non-missing) assessments. Non-optimal imputation techniques, such as Last Observation Carried Forward/Backward (LOCF/B), were not implemented due to the clear observed differences between mean EQ-5D data at 7 days and baseline and between mean EQ-5D data at 14 days and 84 days.

Missing values of the outcome variable QALYs over the active follow-up period (i.e. 84 days) that could not be interpolated as above were dealt with formally using multiple imputation,[50] a statistical technique that imputes with uncertainty based on the observed characteristics of patients or of the disease, i.e. an assumption of missing-at-random. This technique imputes with uncertainty by creating, at a first stage, several plausible imputed datasets and, in a second stage, by combining results obtained from each. Thus, in the first stage, missing values on a covariate of interest are replaced by imputed values using predictions from a model that uses a set of covariates deemed relevant to predict the variable of interest based on those

observations that were not missing. In the second stage, statistical regression methods are fitted to each of the imputed datasets and analysis results are integrated into a single, pooled result. The Multivariate Imputation via Chained Equations (MICE) R package[51] using predictive mean matching was used.[52]

The data collection tool on health-care resource use did not allow distinguishing between no consumption and missing reporting of consumption of health resources. However, given that resource use was collected by investigators in the study, true missingness was assumed negligible and hence no consumption of health resources was assumed where data was missing.

Estimating adjusted mean costs and quality-adjusted life years

Total costs and imputed QALYs were independently regressed on a set of baseline covariates, including treatment group and other potential predictor or treatment-effect modifiers that could be relevant for sub-group analyses. The variables defined for the trial's subgroup analyses (both the pre-specified set and the additional set) were also considered for inclusion here by the clinical advisors to the trial. The final set of covariates was:

- age (categorical, 1- 18-54; 2- 54-72; and 3- >72 years);
- gender (binary, 1- male; 0- female);
- body mass index (BMI, categorical, 1- 18.5-24.9; 2- 25.0-29.9; 3- 30.0-39.9; and 4- >=40 kg/m^2);
- mode of acquisition of infection (categorical, 1- community acquired; 2- nosocomial infection; and 3- healthcare associated);
- Charlson co-morbidity index score (categorical, 1- 0; 2- 1-2; 3- 3-4; and 5- >=5);
- neutrophil count (categorical, 1- <6; 2- 6-9; and >9 $10^9/L$);
- deep infection foci (binary, 1- yes; 0- no);
- endocarditis (binary, 1- yes; 0- no);
- methicillin-resistant *S. aureus* (MRSA, binary, 1- yes; 0- no);
- comatose (binary, 1- yes; 0- no); and
- randomised group.

Continuous variables were categorised using the same thresholds as used in subgroup analyses. In addition, baseline EQ-5D index score was used in the QALY regression as

patient's baseline utilities are likely to be highly correlated with their QALY estimates over the follow-up period, and thus, baseline utility imbalances need to be accounted for.[53]

Five scenarios were analysed: the first, a tentative scenario (models TC and TQ for total costs and QALYs, respectively), assessed the impact of randomised treatment alone in explaining the outcome variables; the second, the base-case, retained all covariates irrespective of their importance to explain the outcome (models 1C and 1Q for total costs and QALYs, respectively). The third scenario follows from the second, but retains/excludes covariates from the full covariate set to select the model of lowest Akaike Information Criteria (AIC).[54] The result is the most parsimonious model based on the AIC statistic, a measure of model quality and goodness of fit (models 1Cp and 1Qp for total costs and QALYs, respectively). A fourth scenario extends the base-case to include interactions with randomised treatment and explore treatment effect modifiers (models 2C and 2Q for total costs and QALYs, respectively). Finally, and similarly to scenario three, the most parsimonious interaction model based on the AIC statistic is obtained (models 2Cp and 2Qp for total costs and QALYs, respectively). The scenarios with and without randomised treatment interactions may have different implications for policy which will be examined.

Total QALYs and total costs captured during 84 days were regressed using a generalised linear modelling (GLM)[55] framework which accounts for the characteristics of the data (i.e. continuously distributed data potentially skewed). Alternative distributions and link functions were tested, and the best fitting based on Akaike's Information Criteria (AIC) was chosen.[54] To determine cost-effectiveness, predicted total costs and total QALYs were evaluated for the mean characteristics of all patients in the trial.

Note that the effect of randomised treatment was modelled independently for costs and health effects, although it is likely that some correlation exists. This should be considered in the interpretation of findings.

Cost-effectiveness and decision uncertainty

To ascertain the cost-effectiveness of a healthcare intervention relative to another, expected health benefits need to be considered against any additional costs expected to be incurred. The fact that a particular technology imposes additional costs means that other activities (that could be financed by these costs) are not undertaken, and this has health consequences to

other patients: the health opportunity costs. If the health gains associated with the technology compensate the health opportunity costs imposed by its additional costs, then using the technology brings net benefits to the NHS and could be recommended for use.

Health opportunity costs are often evaluated from the additional costs imposed by particular technologies using a cost-effectiveness threshold (lambda, λ). Currently the National Institute for Health and Care Excellence (NICE) sets the threshold at £20,000 to £30,000 per QALY gained (although recent work undertaken by the University of York has estimated this to be somehow lower – approximately £13,000 per QALY gained[56]). A new technology is considered cost-effective in relation to existing technologies if the net health benefit (NHB) is $NHB = \Delta B - \Delta C/\lambda > 0$, where λ, ΔB and ΔC represent, respectively, the cost-effectiveness threshold, the incremental benefits and incremental costs.

Decision makers may decide on the provision of services using expected cost-effectiveness findings. However, given the nature of the underlying evidence used, such expectation is not known with certainty. It is hence important that the consequences of uncertainty, and the extent to which it impacts on the adoption decision, are investigated to inform whether further research is needed.[57,58] Uncertainty here stems from the fact that all analyses being based on data collected within this trial, based on a sample of patients and hence generating uncertain estimates of population parameters. The cost-effectiveness analysis can, however, consider such uncertainty over expected costs and benefits (i.e. parameter uncertainty), and evaluate whether the decision to adopt (or reject) the technology is also uncertain i.e. if the Incremental Net Benefit (INB) crosses zero.

To propagate uncertainty in cost-effectiveness analyses, i.e. conduct a probabilistic analysis, Monte Carlo simulation methods are commonly used.[59] With a large number of simulations – in this work we have sampled 10,000 times – it is possible to examine the effect on costs, effects and hence on cost-effectiveness results when the underlying variables are allowed to vary simultaneously across a plausible range according to predefined distributions. Given total costs and benefits were modelled independently, their predicted distributions were also assumed independent. However, costs and benefits were individually modelled using a multivariate regression approach, and therefore to simulate the regression coefficients' variance-covariance matrix was considered in a multivariate Normal framework.[58]

Decisions that are uncertain have expected consequences to the NHS (as well as any attempt to delay or reverse it).[58,60] Acquiring more evidence to support the decision is expected to mitigate these risks, and hence quantifying the risks of uncertainty can inform the value of further evidence collection. The risks and consequences of uncertainty can be quantified using a simple extension of probabilistic analyses called expected value of perfect information (EVPI).[58] The EVPI determines the maximum amount the healthcare system should be willing to pay for more information. In the event the new evidence demonstrates the current decision to be wrong, the decision can be reversed benefiting prospective patients. Individual- and population-level EVPI estimates were estimated at the commonly used cost-effectiveness thresholds referred to above.

Subgroup analysis

Together with base-case and scenario analyses, which explored cost-effectiveness in the whole patient population with SAB, subgroup analyses were also implemented. Subgroup analyses are important as an intervention can prove to be cost-effective for one subgroup of the population and not for another. This might be because the baseline risk of events may differ or because treatment effects or cost implications are different across subgroups (i.e. treatment effect modifying factors). Thus, there may be population health gains from stratifying treatment decisions based on subgroup membership. These analyses explored subgroups based on the regression covariates, namely: age, mode of acquisition of infection, Charlson co-morbidity index score, BMI, deep infection foci, neutrophils and coma status.

Results

A total of 758 participants were recruited: 388 were randomly allocated to receive standard antibiotic therapy (placebo) and 370 to receive adjunctive rifampicin. Baseline characteristics of participants by treatment group can be found in **Table 12.** Note that one rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed. This patient has been excluded from all tables after baseline as they had no post-baseline data, leaving the number in the rifampicin group as 369 rather than 370 in the main Results section.

Resource use and costs

Table 13 provides summary statistics on the trial drug and all other antibiotic therapies received after randomisation during the trial active follow-up period. Fourteen patients (1.8%)

never initiated the trial drug. Active antibiotic therapies administered included flucloxacilin (n=597, 80.9%), ceftriaxone (n=164, 22.2%) and vancomycin (n=144, 19.5%). Open-label rifampicin was used in 52 (13.4%) and 32 (8.7%) patients in the placebo and rifampicin groups, respectively.

Table 12 Characteristics of study participants (health economic analyses)

Baseline characteristic, (n, %) **	Placebo (n=388)	Rifampicin (n=370)*	Total (n=758)*
Gender: male	246 (63.4%)	249 (67.3%)	495 (65.3%)
Age			
at last birthday (years) – mean (median, min-max)	63.0 (66.0, 20.0-100.0)	61.4 (64.0, 18.0-94.0)	62.2 (65.0, 18.0-100.0)
18 – 53 years	126 (32.5%)	125 (33.9%)	251 (33.2%)
54 – 71 years	126 (32.5%)	122 (33.1%)	248 (32.8%)
>= 72 years	136 (35.1%)	123 (33.3%)	259 (34.2%)
BMI			
in kg/m^2 – mean (median, min-max)	27.6 (26.4, 15.2-58.5)	27.2 (26.3, 12.1-73.6)	27.4 (26.3, 12.1-73.6)
< 18.4 kg/m^2	24 (6.2%)	21 (5.7%)	45 (5.9%)
18.5-24.9 kg/m^2	129 (33.2%)	128 (34.7%)	257 (33.9%)
25.0-29.9 kg/m^2	111 (28.6%)	113 (30.6%)	224 (29.6%)
30.0-39.9 kg/m^2	90 (23.2%)	77 (20.9%)	167 (22.1%)
>=40 kg/m^2	23 (5.9%)	21 (5.7%)	44 (5.8%)
Mode of acquisition of infection			
Community acquired	240 (61.9%)	245 (66.4%)	485 (64.1%)
Nosocomial infection (onset ≥48 hrs after admission)	76 (19.6%)	56 (15.2%)	132 (17.4%)
Healthcare associated (all other)	72 (18.6%)	68 (18.4%)	140 (18.5%)
Charlson comorbidity index score			
mean (median, min-max)	2.10 (2.00, 0.00-9.0)	1.97 (1.00, 0.00-11.0)	2.04 (2.00, 0.00-11.0)
0	117 (30.2%)	114 (30.9%)	231 (30.5%)
1-2	143 (36.9%)	154 (41.7%)	297 (39.2%)
3-4	74 (19.1%)	52 (14.1%)	126 (16.6%)
>=5	54 (13.9%)	49 (13.3%)	103 (13.6%)
Neutrophils (10^9/L)			
mean (median, min-max)	8.9 (7.30, 0.00-64.40)	9.25 (7.40, 0.00-83.70)	9.06 (7.30, 0.00-83.70)
<6	151 (38.9%)	135 (36.6%)	286 (37.8%)
6-9	95 (24.5%)	107 (29.0%)	202 (26.7%)
>9	137 (35.3%)	127 (34.4%)	264 (34.9%)
Methicilin resistance	21 (5.4%)	26 (7.0%)	47 (6.2%)
Deep infection foci	159 (41.0%)	142 (38.5%)	301 (39.8%)
Comatose status	43 (11.1%)	37 (10.0%)	80 (10.6%)
Endocarditis	18 (4.6%)	22 (6.0%)	40 (5.3%)

* One rifampicin participant withdrew shortly after randomisation without an enrolment form having been completed: most baseline characteristics (indicated with *) are therefore missing for this one participant. This participant is excluded from all other tables. **unless otherwise specified.

Table 13 Trial drug and active antibiotic therapies received from randomisation through to 84 days (trial active follow-up period), irrespective of dose, frequency and route of administration and indication (health economic analyses)

Patients n (%)	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Trial drug administration during active follow-up period			
n (%)	380 (97.9%)	364 (98.4%)	744 (98.3%)
Antibiotic therapy administration during active follow-up period			
Any antibiotic	382 (98.5%)	356 (96.5%)	738 (97.5%)
Flucloxacillin	315 (82.5%)	282 (79.2%)	597 (80.9%)
Ceftriaxone	81 (21.2%)	83 (23.3%)	164 (22.2%)
Vancomycin	79 (20.7%)	65 (18.3%)	144 (19.5%)
Piperacillin/tazobactam	62 (16.2%)	57 (16.0%)	119 (16.1%)
Gentamicin	45 (11.8%)	40 (11.2%)	85 (11.5%)
Rifampicin	52 (13.6%)	32 (9.0%)	84 (11.4%)
Teicoplanin	36 (9.4%)	41 (11.5%)	77 (10.4%)
Co-amoxiclavulante	46 (12%)	25 (7.0%)	71 (9.6%)
Meropenem	30 (7.9%)	24 (6.7%)	54 (7.3%)
Clindamycin	24 (6.3%)	29 (8.1%)	53 (7.2%)
Ciprofloxacin	29 (7.6%)	22 (6.2%)	51 (6.9%)
Metronidazole	24 (6.3%)	14 (3.9%)	38 (5.1%)
Daptomycin	13 (3.4%)	22 (6.2%)	35 (4.7%)
Doxycycline	16 (4.2%)	16 (4.5%)	32 (4.3%)
Linezolid	13 (3.4%)	12 (3.4%)	25 (3.4%)
Levofloxacin	12 (3.1%)	11 (3.1%)	23 (3.1%)
Trimethroprim	19 (5.0%)	1 (0.3%)	20 (2.7%)
Amoxicllin	10 (2.6%)	5 (1.4%)	15 (2.0%)
Other antibiotics*	67 (17.5%)	47 (13.2%)	114 (15.4%)

Note: Table 4 on 'Backbone' antibiotic treatment shows active 'backbone' antibiotics used to treat the bacteraemia, including antibiotics received before randomisation; numbers therefore differ to those shown here.

*Antibiotics with number of patients below 2% were combined in the "Other antibiotics" category but listed here for completeness: FusidicAcid (1.9%); Clarithromycin (1.8%); Cefuroxime (1.6%); Cotrimoxazole (1.6%); Amikacin (1.2%); Benzylpenicillin (0.9%); Erythromycin (0.9%); Nitrofurantoin (0.7%); Aztreonam (0.5%); Cefalexin (0.5%); Ertapenem (0.5%); Moxifloxacin (0.5%); Azithromycin (0.4%); Ceftazidime (0.4%); Phenoxymethylpenicillin (0.3%); Ticeracillin/clavulanate (0.3%); Tigecycline (0.3%); Cefadrine (0.1%); Cefotaxime (0.1%); Fidaxomicin (0.1%); Norfloxacin (0.1%); Ofloxacin (0.1%); PenicillinV (0.1%); and Temocilin (0.1%).

A summary of the secondary care health resources utilised during trial active follow-up period (i.e. from randomisation to 84 days of follow-up) is provided in **Table 14A**, and of consultations with healthcare providers in **Table 14B**.

All trial patients spent time in hospital, either in the ward or in a critical care unit, with a mean length of stay of 22.3 days post-randomisation (SD=19.7). Patients in the placebo group spent a mean 3.2 days more in the hospital ward than patients in the rifampicin group. Approximately 4% (n=33) of trial patients spent time in a critical care unit. Patients using these units had a mean stay of 11.0 days (SD=14.5). 177 (23%) patients were readmitted to hospital (as day case, to general ward or critical care unit) for any reason. Once readmitted to hospital to general ward or critical care unit, patients in both group spent a mean of 15 days

hospitalised (placebo group: mean 15.9 days, SD=19.0, n=92; rifampicin group: mean 13.9 days, SD=13.5, n=81). The number of hospital procedures and investigations undertaken were fairly balanced between treatment groups and across the different items. The most common hospital procedures were surgical drainage/removal of non-device related focus (n=74, 9.8%, with a mean of 1.3 (SD=0.8) per patient) and radiologically guided biopsy/aspirate/ abscess drainages (n=57, 7.5%, with a mean of 1.6 (SD=1.6) per patient). The most common hospital investigations included CT scans (n=273, 36.0%, with a mean of 1.8 (SD=1.8) per patient), ultrasound scans (other than echocardiogram) (n=237, 31.3%, with a mean of 1.7 (SD=1.1) per patient) and MRI scans (n=234, 30.9%, with a mean of 1.6 (SD=1.0) per patient). 316 (41.7%) trial patients had at least one hospital outpatient visit (**Table 14B**). 275 (36.3%) trial patients had a GP visit.

Table 14 Health resources utilised from randomisation through to 84 days (trial active follow-up period)

A Secondary care health resources

Secondary care health resource*		Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Hospital visits				
Total hospital stay from randomisation to first discharge **	mean (SD) days	23.9 (21.2)	20.5 (17.9)	22.3 (19.7)
Ward	mean (SD) days	23.4 (20.4)	20.2 (17.3)	21.8 (19.0)
	n patients (%)	388 (100.0%)	367 (99.5%)	755 (99.7%)
ITU	mean (SD) days	16.7 (20.9)	14.4 (10.6)	15.6 (16.4)
	n patients (%)	12 (3.1%)	11 (3.0%)	23 (3.0%)
HDU	mean (SD) days	1.8 (0.9)	1.3 (0.5)	1.5 (0.7)
	n patients (%)	4 (1.0%)	7 (1.9%)	11 (1.5%)
Total hospital readmissions	n patients (%)	94 (24.2%)	83 (22.5%)	177 (23.4%)
Hospital readmission (day case) ***	n patients (%)	4 (1.0%)	5 (1.4%)	9 (1.2%)
Hospital readmission (critical care) ***	n patients (%)	6 (1.5%)	4 (1.1%)	10 (1.3%)
Hospital readmission (ward) ***	n patients (%)	90 (23.2%)	80 (21.7%)	170 (22.5%)
Hospital readmission with overnight stay (in ward, ITU or HDU)	mean (SD) days	15.9 (19.0)	13.9 (13.5)	14.9 (16.7)
	n patients (%)	92 (23.7%)	81 (22.0%)	173 (22.9%)
Hospital procedures, including other				
Radiologically guided biopsy/ aspirate/ abscess	mean (SD)	1.4 (1.0)	1.7 (1.9)	1.6 (1.6)
	n patients (%)	25 (6.4%)	32 (8.7%)	57 (7.5%)
Surgical drainage/ removal of non-device related focus	mean (SD)	1.2 (0.4)	1.4 (1.1)	1.3 (0.8)
	n patients (%)	42 (10.8%)	32 (8.7%)	74 (9.8%)
Surgical removal of infected prosthetic device	mean (SD)	1.1 (0.4)	1.0 (0.0)	1.1 (0.2)
	n patients (%)	7 (1.8%)	8 (2.2%)	15 (2.0%)
Cardiac surgery for *S. aureus* endocarditis	mean (SD)	1.4 (0.9)	1.0 (0.0)	1.2 (0.6)
	n patients (%)	5 (1.3%)	6 (1.6%)	11 (1.5%)
Insertion of Hickman line	mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
	n patients (%)	5 (1.3%)	6 (1.6%)	11 (1.5%)

Secondary care health resource*		Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Other procedures	mean (SD)	1.53 (1.0)	1.45 (0.9)	1.49 (1.0)
	n patients (%)	78 (20.1%)	62 (16.8%)	140 (18.5%)
Hospital investigations, including other				
Ultrasound scan (other than echocardiogram)	mean (SD)	1.9 (1.1)	1.6 (1.1)	1.7 (1.1)
	n patients (%)	112 (28.9%)	125 (22.9%)	237 (31.3%)
CT scan	mean (SD)	1.9 (2.1)	1.73 (1.5)	1.83 (1.8)
	n patients (%)	145 (37.4%)	128 (34.7%)	273 (36.1%)
MRI scan	mean (SD)	1.7 (1.1)	1.6 (0.9)	1.7 (1.0)
	n patients (%)	127 (32.7%)	107 (29.0%)	234 (30.9%)
PET scan	mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
	n patients (%)	3 (0.8%)	4 (1.1%)	7 (0.9%)
PET CT scan	mean (SD)	1.1 (0.4)	1.0 (0.0)	1.1 (0.2)
	n patients (%)	7 (1.8%)	10 (2.7%)	17 (2.2%)
Bone scan	mean (SD)	1.0 (0.0)	1.3 (0.5)	1.13 (0.4)
	n patients (%)	9 (2.3%)	6 (1.6%)	15 (2.0%)
White cell scan	mean (SD)	2.0 (n/a)	n/a (n/a)	2.0 (n/a)
	n patients (%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other investigations	mean (SD)	2.5 (3.1)	2.1 (1.7)	2.3 (2.6)
	n patients (%)	31 (8.0%)	26 (7.0%)	57 (7.5%)

* note that summary statistics presented are restricted to the patients who experienced or were subject to interventions listed, e.g. 57 patients were subject to the 'Radiologically guided biopsy/ aspirate/ abscess' hospital procedure with a mean of 1.6 of these procedures per patient and 1.6 standard deviation; ** The mean (SD) time to hospital discharge (in days) from first hospital admission was estimated to be 20.68 (16.18) days. The total hospital stay (on first admission, in days), includes also cases where deaths or withdrawals happened before discharge (at their time of death or withdrawal respectively) and cases where the patient was not discharged at the end of the active follow-up period (duration taken as 84 days). Figure 3 and main Results show total days from admission to discharge, rather than from randomisation to discharge; *** Note that a patient may have had multiple readmissions, and these may have been different i.e. as day case, ward or critical care.

B Consultations with healthcare providers

Consultations with healthcare providers	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
All hospital outpatient visits within follow-up period			
Mean (SD)	4.6 (6.1)	4.6 (5.4)	4.6 (5.8)
n patients (%)	162 (41.8%)	154 (41.7%)	316 (41.7%)
All general practitioner visits within follow-up period			
Mean (SD)	2.9 (3.1)	3.1 (3.4)	3.0 (3.3)
n patients (%)	137 (35.3%)	138 (37.4%)	275 (36.3%)

* note that summary statistics presented are restricted to the patients who experienced the visits listed.

Total costs

Descriptive, unadjusted results

The unadjusted costs per category are shown in **Table 15.** The item with largest mean unadjusted cost was hospital stay in critical care on first admission (£14 625, SD=£20 272, n=34), followed by hospital stay in critical care on readmission (£9 034, SD=£8 036, n=10) and then by hospital procedures (£7 001, SD=£6 936, n=279).

For most categories, the mean unadjusted cost was fairly similar between treatment groups. However, and generally, mean unadjusted cost for hospital stay in the rifampicin group was

lower than in the placebo group. The mean unadjusted cost of hospital ward stay on first admission was greater (by approximately 16%) in the placebo group (£6 973, SD=£6 074, n=388) than in the rifampicin group (£6 025, SD=£5 165, n=367, as two participants allocated to rifampicin were only ever on ITU/HDU). Similarly, mean unadjusted costs relating to hospital stay in critical care was also higher in the placebo group compared to the rifampicin group – although fewer than 5% (n=34) of trial patients were admitted to hospital in these circumstances.

Mainly driven by greater hospital stay, the unadjusted total cost over the active follow-up period for the placebo group was estimated to be mean £1 364 higher than in the rifampicin group (placebo group: £12 861, SD=£12 753 *vs* rifampicin: £11 498, SD=£10 116).

Table 15 Unadjusted costs during trial active follow-up period*

Unadjusted cost (£) *		**Placebo (n=388)**	**Rifampicin (n=369)**	**Total (n=757)**
Treatment costs				
Trial drug **	mean (SD)	£0.0	£30.7 (59.4)	n/a (n/a)
	n patients (%)	380 (97.9%)	364 (98.4%)	744 (98.3%)
All antibiotic therapy	mean (SD)	£862.1 (1 841.8)	£836.0 (1 114.5)	£849.2 (1 525.8)
	n patients (%)	351 (90.5%)	342 (92.7%)	693 (91.5%)
Secondary care health resources utilised				
Hospital first admission				
Hospital ward stay	mean (SD)	£6 973.2 (6 073.4)	£6 025.4 (5 164.6)	£6 512.5 (5 666.1)
	n patients (%)	388 (100.0%)	367 (99.5%)	755 (99.7%)
Hospital stay in critical care (ITU or HDU)	mean (SD)	£17 241.3 (25 719.7)	£12 299.0 (14 209.8)	£14 624.8 (20 272.4)
	n patients (%)	16 (4.1%)	18 (4.9%)	34 (4.5%)
Hospital readmission				
Hospital ward stay	mean (SD)	£4 680.8 (5 659.4)	£4 092.0 (4 038.6)	£4 403.7 (4 957.6)
	n patients (%)	90 (23.2%)	80 (21.7%)	170 (22.5%)
Hospital stay in critical care (ITU or HDU)	mean (SD)	£9 472.5 (9 556.2)	£8 375.3 (6 367.6)	£9 033.6 (8 035.6)
	n patients (%)	6 (1.5%)	4 (1.1%)	10 (1.3%)
Day case	mean (SD)	£481.3 (192.5)	£385.1 (0)	£427.9 (128.4)
	n patients (%)	4 (1.0%)	5 (1.4%)	9 (1.2%)
Hospital procedures	mean (SD)	£7 079.4 (6 810.4)	£6 920.0 (7 088.4)	£7 001.1 (6 936.2)
	n patients (%)	142 (36.6%)	137 (37.1%)	279 (36.9%)
Hospital investigations	mean (SD)	£423.0 (449.2)	£367.9 (398.5)	£395.6 (425.2)
	n patients (%)	249 (64.2%)	246 (66.7%)	495 (65.4%)
Consultations with healthcare providers				
Hospital outpatient visits	mean (SD)	£624.6 (833.4)	£626.1 (734.8)	£625.3 (785.6)
	n patients (%)	162 (41.8%)	154 (41.7%)	316 (41.7%)
General practitioner visits	mean (SD)	£104.3 (111.6)	£110.1 (123.1)	£107.2 (117.3)
	n patients (%)	137 (35.3%)	138 (37.4%)	275 (36.3%)
Total costs over the follow-up period	mean (SD)	£12 861.3 (12 753.1)	£11 497.8 (10 116.0)	£12 196.6 (11 555.7)
	n patients (%)	388 (100.0%)	369 (100.0%)	757 (100.0%)

* These statistics are based on available cases, i.e. missing responses were assumed to be zero when there was at least one non-missing response; ** Placebo was assumed to be of £0 cost.

Unadjusted costs per treatment group are, alternatively, presented by time intervals in **Table 16.** As some healthcare resource consumption within the active follow-up period had no associated date, either because assessment date or form date was not available, the mean unadjusted costs of unspecified date are also presented.

During the first 2 weeks after randomisation, similar estimated costs were observed between treatment groups with mean unadjusted costs of approximately £5 880 and £6 293, respectively for rifampicin and placebo groups. During the following 10 weeks and until the end of active follow-up, the healthcare allocated to the placebo group was estimated to cost mean £787 more than the care required by patients in the rifampicin group (rifampicin: £4 524 *vs* placebo: £5 311). Similarly, unadjusted mean costs of healthcare during active follow-up period but of no specified date were higher in the placebo group relative to the rifampicin group.

Table 16 Unadjusted costs by time period*

Unadjusted cost (£)	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
From baseline to day 14			
Mean (SD)	£6 293.1 (8 259.3)	£5 879.7 (7 606.4)	£6 088.6 (7 945.2)
n patients (%)	380 (97.9%)	369 (100.0%)	749 (98.9%)
Days 15 to 84			
Mean (SD)	£5 310.5 (8 574.3)	£4 523.8 (6 855.7)	£4 927.0 (7 789.0)
n patients (%)	285 (73.5%)	247 (66.9%)	532 (70.3%)
*Day unspecified, within follow-up period***			
Mean (SD)	£2 130.9 (4 643.7)	£1 952.1 (3 661.9)	£2 045.8 (4 201.3)
n patients (%)	192 (49.5%)	169 (45.8%)	361 (47.7%)

* These statistics are based on available cases, i.e. missing responses were assumed to be zero when there was at least one non-missing response; ** Day unspecified implies that a date of assessment or CRF date was not available.

Adjusted results

Base-case model (model 1C)

A series of distributional and functional assumptions were modelled. Models assuming observed data followed a gamma distribution with a log link function produced the lowest AIC statistics (highlighted in bold) for the different scenarios (**Table 33** in **Appendix 2**). Note that smaller AIC values indicate better model quality of fit. Thus, for the base-case (model 1C) and the treatment interactions model (model 2C) a gamma distribution with a log link function was chosen.

The results of the regression models TC and 1C are presented in **Table 17.** Additionally, the results of model 1Cp, the most parsimonious model based on AIC using the covariate set of model 1C, are also presented.

Results showed that no evidence exists that indicate that healthcare costs differed between the rifampicin and placebo groups (p-value=0.14 in model 1C). Note that, given the non-linear specification of the model, coefficients are interpreted multiplicatively rather than additively. Thus, and for instance, to obtain predicted total costs with model 1C we have that, a patient at the reference category for all factors is associated with expected costs of £8 752 [calculated as *exp(9.08)*]. For the rifampicin group, total expected costs are £7 956 [calculated as *exp(-0.10+9.08)= exp(9.08)*exp(-0.10)*= £8 752 * 0.91].

Patients with nosocomial infections, with deep foci infection, with endocarditis, with neutrophils count above $6x10^9$/L and in a coma had significantly higher healthcare costs than those in the respective reference categories (community-acquired infections, without deep foci, without endocarditis, with neutrophils $<6x10^9$/L, with consciousness, respectively). Model 1Cp retained only the above mentioned variables, reinforcing that this reduced covariate set is sufficient to explain variation in healthcare resource consumption.

Table 17 Modelling total costs over the active follow-up period (84 days) – base-case and parsimonious model results

Model specification	**Model TC**	**Model 1C**	**Model 1Cp**
Type of regression model		Gamma, log link	
Equation		Log Total costs	
Covariates (baseline)	coefficient [SE]	coefficient [SE]	coefficient [SE]
Randomised treatment (1-rifampicin; 0-placebo)	-0.11 [0.07]	-0.10 [0.07]	---
Age, 54-71 years	---	0.08 [0.08]	---
Age, >=72 years	---	0.04 [0.08]	---
Gender (1-male;0-female)	---	-0.06 [0.07]	---
Acquisition, nosocomial infection	---	0.35 [0.09] ***	0.37 [0.09] ***
Acquisition, healthcare associated	---	0.06 [0.09]	0.07 [0.09]
Charlson index, 1-2	---	0.11 [0.08]	---
Charlson index, 3-4	---	0.01 [0.11]	---
Charlson index, >=5	---	0.06 [0.11]	---
BMI, 18.5-24.9 kg/m^2	---	-0.23 [0.14]	---
BMI, 25.0-29.9 kg/m^2	---	-0.09 [0.15]	---
BMI, 30.0-39.9 kg/m^2	---	-0.14 [0.15]	---
BMI, >=40 kg/m^2	---	-0.11 [0.19]	---
Deep focus (1-yes; 0-no)	---	0.36 [0.07] ***	0.35 [0.07] ***
Endocarditis (1-yes; 0-no)	---	0.50 [0.15] **	0.43 [0.16] **
Methicilin resistance	---	0.18 [0.14]	---
Neutrophils, 6-9 10^9/L	---	0.12 [0.08]	0.09 [0.08]
Neutrophils, >9 10^9/L	---	0.30 [0.08] ***	0.29 [0.08] ***
Comatose (1-yes; 0-no)	---	0.28 [0.11] *	0.27 [0.11] *
Intercept	9.46 [0.05] ***	9.08 [0.16] ***	8.97 [0.07] ***
Observations	757	730	730

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1.

Model 1C predictions can be found in **Table 18,** first set of results. For the mean patient in the trial (**Table 12**) across all covariates used in the regression, the weighted mean predicted total cost for the placebo group was £1 092 higher than in the rifampicin group (rifampicin: £11 050, SE=£510 *vs* placebo: £12 142, SE=£546). Model 1Cp total cost predictions were similar, in magnitude, to model 1C.

Table 18 Predicted total costs over the follow-up period by treatment group

Cost predictions (£)	Model	Placebo	Rifampicin
Mean predicted total costs [95% CI]	Model 1C	£12 142 [£11 194, £13 249]	£11 050 [£10 089, £12 068]
Median predicted total costs [interquartile range]		£12 129 [£11 778 – £12 500]	£11 040 [£10 708 – £11 389]
Mean predicted total cost difference [95% CI]		-£1 092 [-£2 564, -£371.7]	
Mean predicted total costs [95% CI]	Model 2C	£11 969 [£10 962, £13 040]	£10 900 [£9 947, £11 925]
Median predicted total costs [interquartile range]		£11 952 [£11 604 – £12 321]	£10 889 [£10 556 – £11 233]
Mean predicted total cost difference [95% CI]		-£1 068 [-£2 510, £392]	

Scenario analysis – consideration of treatment effect modifiers (model 2C)

Results of model 2C can be found in **Table 19** Results of modelling total costs over the active follow-up period (84 days) – exploring treatment effect modifiers through treatment interactions model and a parsimonious interaction model**.** The scenario analysis using a model with treatment interactions (model 2C), irrespective of their statistical significance, showed that, in general, the associations observed in model 1C persisted. Note that the BMI category of 18.5 to 24.9 kg/m^2 was now associated with lower healthcare costs relative to the reference BMI category (<18.5 kg/m^2). The predicted total costs for a patient at the reference category for all other factors in the rifampicin group in model 2C are: *exp(-0.43+9.23)*= £6 635, while for the placebo group: *exp(9.23)*= £10 240.

Model 2Cp restricted model 2C to the covariates and potential effect modifiers that represent the most parsimonious model. Results for this model are also shown in **Table 19** Results of modelling total costs over the active follow-up period (84 days) – exploring treatment effect modifiers through treatment interactions model and a parsimonious interaction model**.** This model produced similar findings to the model 1Cp, with the exception that age and randomised treatment interaction with age were now retained. Patients in the rifampicin group

and in the age category between 54 and 71 years of age were associated with higher healthcare costs (£8 602, calculated as *exp(9.00-0.16-0.05+0.27)*] than those in the placebo group (£7 726, calculated as *exp(9.00-0.05)*]). The predicted total costs for a patient at the reference category for all other factors in the rifampicin group in model 2Cp was: *exp(9.00-0.16)*= £6 908, while for the placebo group: *exp(9.00)*= £8 128.

Model 2C weighted total cost predictions considering the mean patient in the trial across all covariates can be found in **Table 18.** Overall, total cost predictions are similar to the ones obtained in model 1C, the base case model. Model 2Cp total cost predictions (not shown) for the placebo group were £1 239 higher than in the rifampicin group. Total cost predictions for each patient subgroup and randomised treatment are presented in the cost-effectiveness and decision uncertainty section.

Table 19 Results of modelling total costs over the active follow-up period (84 days) – exploring treatment effect modifiers through treatment interactions model and a parsimonious interaction model

Model specification	**Model 2C**	**Model 2Cp**
Type of regression model	Gamma, log link	
Equation	Log Total costs	
Covariates (baseline)	coefficient [SE]	coefficient [SE]
Randomised treatment (1-rifampicin; 0-placebo)	-0.43 [0.31]	-0.16 [0.11]
Age, 54-71 years	-0.05 [0.11]	-0.05 [0.12]
Age, >=72 years	0.05 [0.12]	0.08 [0.11]
Gender (1-male;0-female)	-0.12 [0.09]	---
Acquisition, nosocomial infection	0.38 [0.12] **	0.36 [0.09] ***
Acquisition, healthcare associated	0.11 [0.12]	0.09 [0.09]
Charlson index, 1-2	0.13 [0.11]	---
Charlson index, 3-4	0.02 [0.14]	---
Charlson index, >=5	0.25 [0.15] .	---
BMI, 18.5-24.9 kg/m^2	-0.41 [0.20] *	---
BMI, 25.0-29.9 kg/m^2	-0.35 [0.20] .	---
BMI, 30.0-39.9 kg/m^2	-0.28 [0.20]	---
BMI, >=40 kg/m^2	-0.41 [0.26]	---
Deep focus (1-yes; 0-no)	0.49 [0.10] ***	0.33 [0.07] ***
Endocarditis (1-yes; 0-no)	0.43 [0.22] .	0.48 [0.16] **
Methicillin resistance	0.22 [0.21]	---
Neutrophils, 6-9 10^9/L	0.15 [0.12]	0.09 [0.08]
Neutrophils, >9 10^9/L	0.30 [0.11] **	0.29 [0.08] ***
Comatose (1-yes; 0-no)	0.16 [0.15]	0.25 [0.11] *
Treatment * Age, 54-71 years	0.25 [0.16] .	0.27 [0.16] .
Treatment * Age, >=72 years	-0.05 [0.17]	-0.06 [0.16]
Treatment * Gender (1-male;0-female)	0.11 [0.14]	---
Treatment * Acquisition, nosocomial infection	-0.06 [0.18]	---
Treatment * Acquisition, healthcare associated	-0.06 [0.18]	---
Treatment * Charlson index, 1-2	-0.06 [0.16]	---
Treatment * Charlson index, 3-4	0.005 [0.21]	---
Treatment * Charlson index, >=5	-0.36 [0.21] .	---
Treatment * BMI, 18.5-24.9 kg/m^2	0.37 [0.28]	---
Treatment * BMI, 25.0-29.9 kg/m^2	0.51 [0.29]	---
Treatment * BMI, 30.0-39.9 kg/m^2	0.27 [0.30] .	---

Model specification	Model 2C	Model 2Cp
Treatment * BMI, >=40 kg/m^2	0.61 [0.37]	---
Treatment * Deep focus (1-yes; 0-no)	-0.25 [0.14] .	---
Treatment * Endocarditis (1-yes; 0-no)	0.19 [0.31]	---
Treatment * Methicillin resistance	-0.10 [0.28]	---
Treatment * Neutrophils, 6-9 10^9/L	-0.04 [0.16]	---
Treatment * Neutrophils, >9 10^9/L	0.02 [0.15]	---
Treatment * Comatose (1-yes; 0-no)	0.17 [0.22]	---
Intercept	9.23 [0.22] ***	9.00 [0.10] ***
AIC	15 105	15 080
Observations	730	730

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1.

Health benefits

Utility and quality-adjusted life-years (unadjusted and not using multiple imputation)

At baseline, there were approximately 10% (n=80) comatose patients and 3% (n=20) of patients unable or unwilling to provide answers to the EQ-5D questionnaire due to their poor health. Descriptive statistics on HRQoL at different assessment times can be found in **Table 20A.** Observed EQ-5D scores by domain/level and by time period can be found in **Table 34** in **Appendix 2**.

Table 20 Unadjusted EQ-5D index scores and QALYs by treatment group

A. Unadjusted EQ-5D index scores over time

Unadjusted EQ-5D index score *	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Baseline			
n patients (%)	381 (98.2%)	365 (98.9%)	746 (98.5%)
- Number responded	329 (84.8%)	317 (85.7%)	646 (85.2%)
- Number in coma	43 (11.1%)	37 (10.0%)	80 (10.5%)
- Number unwilling/unable	9 (2.3%)	11 (3.0%)	20 (2.6%)
Mean of unadjusted EQ-5D index score (SD) *	0.09 (0.35)	0.12 (0.34)	0.10 (0.34)
Day 7			
n patients (%)	314 (80.9%)	293 (79.4%)	608 (80.3%)
- Number responded	283 (72.9%)	258 (69.9%)	542 (71.6%)
- Number in coma	24 (6.2%)	24 (6.5%)	48 (6.3%)
- Number unwilling/unable	7 (1.8%)	11 (3.0%)	18 (2.4%)
- Number died	7 (1.8%)	13 (3.5%)	20 (2.6%)
Mean of unadjusted EQ-5D index score (SD) *	0.19 (0.34)	0.19 (0.35)	0.19 (0.34)
Day 14			
n patients (%)	240 (61.9%)	213 (57.7%)	453 (59.8%)
- Number responded	215 (55.4%)	188 (50.9%)	403 (53.2%)
- Number in coma	20 (5.2%)	18 (4.9%)	38 (5.0%)
- Number unwilling/unable	5 (1.3%)	7 (1.9%)	12 (1.6%)
- Number died	17 (4.4%)	25 (6.8%)	42 (5.5%)
Mean of unadjusted EQ-5D index score (SD) *	0.20 (0.34)	0.17 (0.32)	0.19 (0.33)
Day 84			
n patients (%)	280 (72.2%)	251 (68.0%)	531 (70.1%)
- Number responded	273 (70.4%)	244 (66.1%)	516 (68.2%)
- Number in coma	2 (0.5%)	2 (0.5%)	4 (0.5%)

- Number unwilling/unable	5 (1.5%)	5 (1.4%)	10 (1.5%)
- Number died	56 (14.4%)	56 (15.2%)	112 (14.8%)
Mean of unadjusted EQ-5D index score (SD) *	0.29 (0.31)	0.32 (0.28)	0.30 (0.29)

*Deceased patients received an EQ-5D index score of *0*; Comatose patients received an EQ-5D index score of *-0.402*; Patients reported to be unable/unwilling to provide EQ-5D answers received an EQ-5D index score of *-0.261*, corresponding to the bottom decile of the EQ-5D index score distribution of all trial patients for which a EQ-5D index score was available.
** Deceased patients, in a coma or unable/unwilling to provide EQ-5D answers were allocated scores as described in footnote *.

B Unadjusted total QALYs (not using multiple imputation, but including hard imputations for coma/unwilling/unable to complete and death)

Unadjusted total QALYs	Placebo (n=388)	Rifampicin (n=369)	Total (n=757)
Mean (SD)	0.054 (0.063)	0.059 (0.059)	0.057 (0.061)
n patients (%)	275 (70.9)	249 (67.3)	524 (69.1)

Descriptive statistics of the EQ-5D index scores (unadjusted) show that the mean score is fairly balanced across treatment groups, irrespective of time point of assessment. The baseline unadjusted mean EQ-5D index score was 0.10 (SD=0.34, n=746), reflecting the very poor quality of life of patients affected with *S. aureus* bacteraemia. At 7 days the unadjusted mean EQ-5D index score was 0.19 (SD=0.34, n=608) and at 14 days also 0.19 (SD=0.33, n=453). At this assessment point, 42 (5.5%) patients had died and hence were allocated an EQ-5D index score of *0*. In interpreting these figures, care is needed as 40% fewer patients completed the EQ-5D questionnaire at 14 days. At the end of the active follow-up (84 days) the mean unadjusted EQ-5D index score was 0.30 (SD=0.29, n=531). Again, at this point 112 (14.8%) of patients were deceased and received an EQ-5D index score of *0*. Although only about 70% (n=531, including values allocated for deceased/comatose/unable to answer patients as per Methods, denoted "hard" imputations below) of the total number of patients that were recruited into the trial completed an EQ-5D at 84 days, it shows that the selective group of patients for whom a EQ-5D index score at 84 days was obtained had a better (higher) mean EQ5D score than the remaining individuals, at baseline. Distributions of EQ-5D index score at baseline, 7, 14 and 84 days (not using multiple imputation, but including hard imputations for coma/unwilling/unable to complete and death) are shown in **Figure 22** in **Appendix 4**.

The unadjusted total QALYs (over the whole of the follow-up period, including hard imputed values as per Methods) are presented in **Table 20B.** We highlight again that results correspond to only about 70% of the sample as information for remaining patients was missing. Given that the period of assessment is 84 days (i.e. 3 months = a quarter of a year), the maximum total QALYs that we can observe is 0.25. Thus, the distribution of total QALYs

will be inherently be both left and right truncated. Mean unadjusted total QALYs were similar between treatment groups, with a total mean QALY of 0.06 (SE=0.06). The distribution of total unadjusted total QALYs, including hard imputed values as per Methods, can be seen in **Figure 19A**.

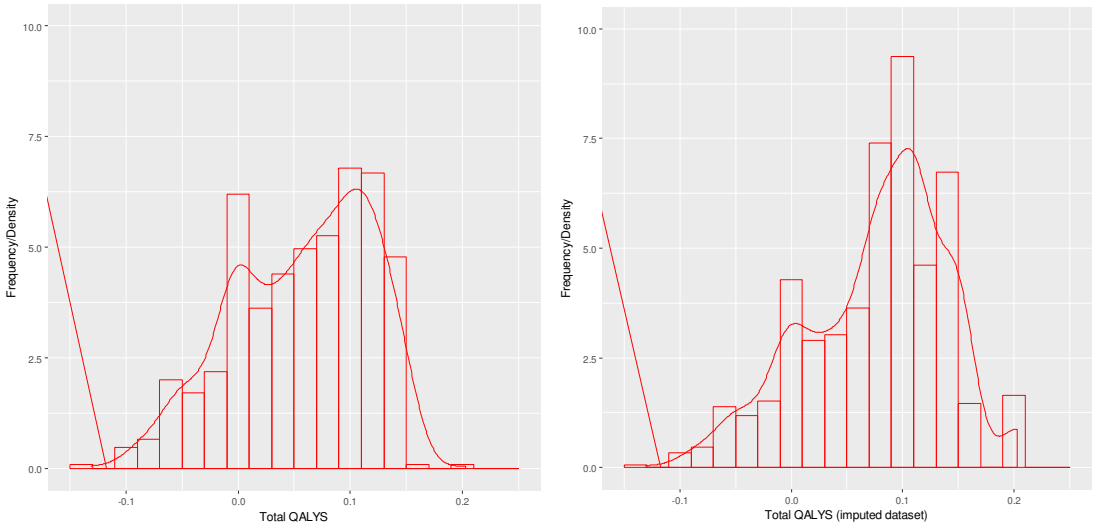


Figure 19 A. Distribution of total QALYs; and B. Distribution of imputed total QALYs from one randomly selected imputed dataset using multiple imputation techniques

Quality-adjusted life-years (using multiple imputation)

A multiple imputation procedure was used to impute missing total QALYs at 84 days, which occurred in approximately 31% of the sample. Following suggestion from the literature in which the number of imputations should be similar to the percentage of cases that are incomplete,[61,62] 30 imputations of 20 iterations each were performed. Mode of acquisition of infection, Charlson co-morbidity index score, BMI, deep infection foci, endocarditis, neutrophil count, coma status and EQ-5D index score were the baseline patient characteristics used as predictors by the imputation model. This process generated 30 different datasets with a calculated imputed outcome variable (i.e. total QALYs at 84 days). The distribution of total QALYs at 84 days for one of the imputed datasets, randomly chosen, can be seen in **Figure 19B**. On these multiple imputed datasets, alternative GLM models for the total QALYs at 84 days were considered. As for the cost data, the null model, a model only with randomised treatment (model TQ) and a model with all covariates were implemented (model 1Q). A regression model assuming a normally distributed outcome with identity link (i.e. ordinary least squares model) was chosen (AIC statistic in model 1Q: -2 109). Other modelling distributional assumption tested either did not run or did not converge.

Base-case model (model 1Q)

The results of the base case model (model 1Q) are shown in **Table 21.** These results are complemented with results of the model considering randomised treatment only (model TQ, first column). Regression models presented are linear and therefore additive, so coefficients can be interpreted directly to assess their impact on the outcome variable. In the model 1Q, being randomised to rifampicin was associated with slightly higher total QALYs (mean 0.004, SE=0.004) than being randomised to placebo, although this association was not statistically significant (p=0.40, similar for model TQ). As expected, the EQ-5D index score at baseline was one of the main predictors of total QALYs accrued over 84 days, with one unit higher baseline EQ-5D estimated to be associated with higher total QALYs (model 1Q: mean difference of 0.06, 95% CI 0.05 to 0.08). Conversely, those of 72 years or older (model 1Q: -0.043, 95% CI -0.072 to -0.014), having any co-morbidities as indicated in the Charlson co-morbidity index (gradient from -0.015, 95% CI -0.027 to -0.003 for index scores of 1-2, up to -0.024, 95% CI -0.041 to -0.006, for higher index scores) and being in a coma (-0.020, 95% CI -0.037 to -0.004) was associated with significantly lower total QALYs. These covariates, together with methicillin resistance and neutrophil count, were retained in model 1Qp, showing that the latter are also relevant to explain variation in total QALYs.

Table 21 Modelling total QALYs at end of active follow-up period (84 days) using multiple imputation – base-case and parsimonious model results

Model specification	**Model TQ**	**Model 1Q**	**Model 1Qp [+]**
Type of regression model	OLS		
Equation	Total QALYs (imputed)		
Covariates (baseline)	coefficient [SE]	coefficient [SE]	coefficient [SE]
EQ-5D index baseline score	---	0.064 [0.008] ***	0.064 [0.008] ***
Randomised treatment (1-rifampicin; 0-placebo)	0.007 [0.005]	0.004 [0.004]	---
Age, 54-71 years	---	-0.026 [0.020]	-0.027 [0.020] ***
Age, >=72 years	---	-0.043 [0.014] **	-0.044 [0.014] **
Gender (1-male;0-female)	---	0.004 [0.005]	---
Acquisition, nosocomial infection	---	-0.005 [0.006]	---
Acquisition, healthcare associated	---	-0.001 [0.006]	---
Charlson index, 1-2	---	-0.015 [0.006] **	-0.015 [0.006] *
Charlson index, 3-4	---	-0.019 [0.008] **	-0.020 [0.007] **
Charlson index, >=5	---	-0.024 [0.009] **	-0.024 [0.009] **
BMI, 18.5-24.9 kg/m^2	---	0.005 [0.010]	---
BMI, 25.0-29.9 kg/m^2	---	0.005 [0.010]	---
BMI, 30.0-39.9 kg/m^2	---	0.010 [0.011]	---
BMI, >=40 kg/m^2	---	0.004 [0.013]	---
Deep focus (1-yes; 0-no)	---	0.0004 [0.005]	---
Endocarditis (1-yes; 0-no)	---	0.003 [0.011]	---
Methicilin resistance	---	-0.027 [0.020]	-0.024 [0.021]
Neutrophils, 6-9 10^9/L	---	0.004 [0.006]	0.005 [0.006]
Neutrophils, >9 10^9/L	---	-0.010 [0.006] .	-0.011 [0.006] .
Comatose (1-yes; 0-no)	---	-0.020 [0.008] *	-0.020 [0.008] *

Intercept	0.076 [0.009] ***	0.104 [0.012] ***	0.115 [0.006] ***
Observations	757	724	724

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1. + 30 parsimonious models were obtained, one for each imputed dataset. The covariate set retained in the parsimonious models was slightly different across models. Thus, results shown use a majority rule, i.e. when the covariate was retained 3 or more times.

For the mean patient in the trial across all covariates used in the regression, the weighted mean predicted total QALYs for the placebo group was similar in the rifampicin and the placebo groups (**Table 22,** first set of results). As expected, due to model linearity, the difference in predicted total QALYs between treatment groups was estimated to be mean 0.004 (SE=0.004). Results of the sensitivity analysis on patients unable/unwilling to provide EQ-5D answers can be found in **Tables 35, 36 and 37** in **Appendix 2**.

Table 22 Predicted total QALYS at the end of the active follow-up period by treatment group (using multiple imputation)

HRQoL predictions (QALYS)	Model	Placebo	Rifampicin
Mean predicted total QALYs [SE]	Model 1Q	0.077 [0.008]	0.080 [0.009]
Median predicted total QALYs [interquartile range]		0.077 [0.071 – 0.082]	0.080 [0.074 – 0.086]
Mean predicted total QALYs difference		0.004 [0.004]	
Mean predicted total QALYs [SE]	Model 2Q	0.076 [0.010]	0.080 [0.013]
Median predicted total QALYs [interquartile range]		0.076 [0.070 – 0.083]	0.080 [0.071 – 0.088]
Mean predicted total QALYs difference		0.004 [0.003]	

Scenario analysis – consideration of treatment effect modifiers (model 2Q)

As for total costs, a scenario analysis was implemented for total QALYs (model 2Q) considering treatment interactions. The results of this scenario analysis can be found in **Table 23.** In general, similar results to model 1Q were obtained. Following model 1Q, model 2Q did not find treatment to be significantly associated with total QALYs. Model 2Qp results (also in **Table 23)** show that the most parsimonious model retained the following covariates as important to explain the outcome variable: EQ-5D baseline score, age, Charlson index, methicillin resistance, neutrophil count and coma status. Thus, randomised treatment and randomised treatment interactions were not selected for the most parsimonious model based on AIC statistics. As for model 1Q, and considering the mean trial patient, as no statistically significant difference was found between treatment groups, both groups had similar mean total QALYs (**Table 22,** second set of results). Total QALYs predictions for each patient subgroup and randomised treatment are presented in the cost-effectiveness and decision uncertainty section.

Table 23 Modelling total QALYs at end of follow-up period (multiple imputation)

Model specification	**Model 2Q**	**Model 2Qp**
Type of regression model	OLS	
Equation	Total QALYs (imputed)	
Covariates (baseline)	coefficient [SE]	coefficient [SE]
EQ-5D index score	0.064 [0.011] ***	0.064 [0.008] ***
Randomised treatment (1-rifampicin; 0-placebo)	0.016 [0.022]	---
Age, 54-71 years	-0.028 [0.020]	-0.027 [0.020]
Age, >=72 years	-0.041 [0.014] **	-0.044 [0.014] **
Gender (1-male;0-female)	0.005 [0.007]	---
Acquisition, nosocomial infection	-0.002 [0.008]	---
Acquisition, healthcare associated	-0.005 [0.009]	---
Charlson index, 1-2	-0.011 [0.008]	-0.015 [0.006] *
Charlson index, 3-4	-0.017 [0.010] .	-0.020 [0.007] **
Charlson index, >=5	-0.012 [0.010]	-0.024 [0.009] **
BMI, 18.5-24.9 kg/m^2	-0.0003 [0.014]	---
BMI, 25.0-29.9 kg/m^2	0.004 [0.014]	---
BMI, 30.0-39.9 kg/m^2	0.015 [0.014]	---
BMI, >=40 kg/m^2	0.015 [0.018]	---
Deep focus (1-yes; 0-no)	0.008 [0.007]	---
Endocarditis (1-yes; 0-no)	-0.005 [0.016]	---
Methicillin resistance	-0.020 [0.028]	-0.024 [0.021]
Neutrophils, 6-9 10^9/L	0.010 [0.009]	0.005 [0.006]
Neutrophils, >9 10^9/L	-0.018 [0.008] *	-0.011 [0.006] .
Comatose (1-yes; 0-no)	-0.020 [0.012] .	-0.020 [0.008] *
Treatment * EQ-5D index score	0.003 [0.016]	---
Treatment * Age, 54-71 years	0.005 [0.011]	---
Treatment * Age, >=72 years	-0.007 [0.011]	---
Treatment * Gender (1-male;0-female)	-0.003 [0.009]	---
Treatment * Acquisition, nosocomial infection	-0.010 [0.012]	---
Treatment * Acquisition, healthcare associated	0.008 [0.013]	---
Treatment * Charlson index, 1-2	-0.007 [0.011]	---
Treatment * Charlson index, 3-4	-0.003 [0.016]	---
Treatment * Charlson index, >=5	-0.024 [0.016]	---
Treatment * BMI, 18.5-24.9 kg/m^2	0.009 [0.020]	---
Treatment * BMI, 25.0-29.9 kg/m^2	0.003 [0.020]	---
Treatment * BMI, 30.0-39.9 kg/m^2	-0.009 [0.021]	---
Treatment * BMI, >=40 kg/m^2	-0.020 [0.026]	---
Treatment * Deep focus (1-yes; 0-no)	-0.018 [0.011] .	---
Treatment * Endocarditis (1-yes; 0-no)	0.019 [0.021]	---
Treatment * Methicillin resistance	-0.013 [0.022]	---
Treatment * Neutrophils, 6-9 10^9/L	-0.007 [0.011]	---
Treatment * Neutrophils, >9 10^9/L	0.015 [0.011]	---
Treatment * Comatose (1-yes; 0-no)	-0.001 [0.017]	---
Intercept	0.098 [0.015] ***	0.115 [0.006] ***
Observations	724	724

Statistical significance: ***, α<0.001; **, α<0.01; *, α<0.05; ., α<0.1. + 30 parsimonious models were obtained, one for each imputed dataset. The covariate set retained in the parsimonious models was slightly different across models. Thus, results shown use a majority rule, i.e. when the covariate was retained 3 or more times.

Cost-effectiveness and decision uncertainty

The results presented above on the analysis of costs and health outcomes (QALYs) showed that participants randomised to receive rifampicin for the treatment of *S. aureus* bacteraemia were expected to attain higher QALYs over the duration of the trial, and were expected to incur lower costs than those participants allocated to receive placebo. These results were not, however, statistically significant.

Considering the mean total costs and mean total QALYs at face value, adjunctive rifampicin could promote relevant cost savings over an 84-day time horizon without compromising health outcomes, and that actually there may be even positive, although small, implications to total QALYs (**Table 24**). This means that rifampicin dominates placebo, that is, it costs less but provides additional health benefits compared to placebo. If releasing £20 000 to the NHS is assumed to result in 1 additional QALY (the cost-effectiveness threshold), the mean incremental net health benefit (INHB) of adjunctive rifampicin is approximately 0.06 QALY (SE=0.04 QALY).

Table 24 Cost-effectiveness – base-case and scenario analysis results

Cost-effectiveness outcomes – mean [SE]		**Placebo**	**Rifampicin**
Base case results (using results from regression models 1C and 1Q)			
Predicted total costs (£)		£12 142 [546.0]	£11 050 [509.7]
Predicted total QALYs		0.077 [0.008]	0.080 [0.009]
Incremental predicted total costs (£)		-£1 092 [749.8]	
Incremental predicted total QALYs		0.004 [0.004]	
ICER (£/QALY gained)		Rifampicin dominates, i.e. costs less and has positive health benefits in relation to placebo	
Incremental net health benefit *	£13 000/QALY	0.088 [0.058]	
	£20 000/QALY	0.058 [0.038]	
	£30 000/QALY	0.040 [0.025]	
Probability of being cost-effective *	£13 000/QALY	0.07	0.93
	£20 000/QALY	0.06	0.94
	£30 000/QALY	0.06	0.94
Scenario analysis results (using results from regression models 2C and 2Q)			
Predicted total costs (£)		£11 969 [535.8]	£10 900 [500.2]
Predicted total QALYs		0.076 [0.010]	0.080 [0.013]
Incremental predicted total costs (£)		-£1 068 [726.6]	
Incremental predicted total QALYs		0.004 [0.003]	
ICER (£/QALY gained)		Rifampicin dominates, i.e. costs less and has positive health benefits in relation to placebo	
Incremental net health benefit *	£13 000/QALY	0.086 [0.056]	
	£20 000/QALY	0.057 [0.037]	
	£30 000/QALY	0.039 [0.024]	
Probability of being cost-effectiveness *	£13 000/QALY	0.06	0.94
	£20 000/QALY	0.06	0.94
	£30 000/QALY	0.06	0.94

* at cost-effectiveness thresholds of £13 000, £20 000 and £30 000 per QALY gained, respectively.

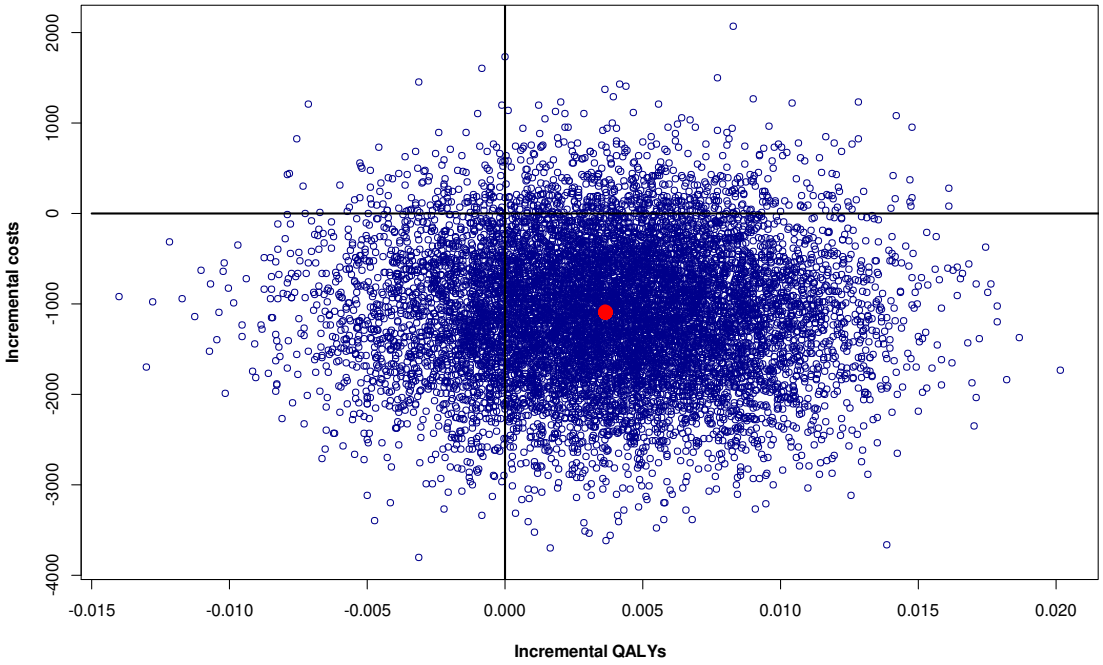


Figure 20 Cost-effectiveness plane for the base case results

Figure 20 shows the cost-effectiveness plane using results from the Monte Carlo simulation to represent uncertainty over incremental mean costs and QALYs (joint density plot). Each blue dot represents a simulated incremental cost and QALY pair; the cloud of blue points is representative of the uncertainty around the cost-effectiveness outcomes. The red dot displays the mean incremental costs and effects. The majority of blue points lay in the 4th quadrant of negative incremental costs and positive incremental benefits. The ARREST trial data shows rifampicin is likely to be less costly and is associated with small QALY gains (although uncertain) in the 84 days of follow-up (post-randomisation). This suggests rifampicin is cost-effective with very little associated uncertainty, i.e. a very high probability of being cost-effective (93-94%). Similar results to the base-case were found for the scenario analysis (**Table 24**).

Considering a technology time horizon of 10 years and an annual effective population of 12,500 patients per year in the UK [1], the expected value of perfect information (EVPI) for the MRSA/MSSA bacteraemia population is estimated to be approximately £2 million at the commonly used cost-effectiveness thresholds. This estimate represents the maximum amount the healthcare system should be willing to pay for further information and resolve identified uncertainties. At the individual-level and for the same cost-effectiveness threshold values, the EVPI is estimated to be approximately £20 per MRSA/MSSA patient.

Subgroup-analysis

This subgroup analysis uses the exploratory models with interactions (models 2C and 2Q) presented above to evaluate the evidence of ARREST on whether costs and QALY impacts of an *S. aureus* episode differ with patient characteristics, and to evaluate whether there are subgroups where the cost-effectiveness profile of rifampicin differs.

In terms of the costs of an *S. aureus* episode, the results of this analysis (**Table 25**) suggests that patients presenting with a nosocomial infection, low BMI, deep infection foci, endocarditis and MRSA have higher episode costs (above £15000 per episode) than their counterparts. In what concerns QALYs, high neutrophil count (>9 10^9/L), MRSA or older than 72 years of age at presentation were factors associated with lower overall QALYs. With respect to the impact of baseline patient characteristics on the cost-effectiveness of rifampicin, the subgroup analysis suggests that, for most subgroups rifampicin offers net health gains in relation to placebo. Those where rifampicin may not offer net health gains in relation to placebo are: age group between 54 and 72 years, BMI between 25.0-29.9 kg/m^2 and above 40 kg/m^2, endocarditis and coma. Note that this analysis is exploratory and findings should be interpreted with care.

Table 25 Cost-effectiveness results by treatment group and for a range of baseline characteristics considering the base-case scenario

Cost-effectiveness outcomes by subgroups *	Placebo (mean [SE])		Rifampicin (mean [SE])		INHB**	PCE Rifampicin ***
	Costs	QALYs	Incr. Costs	Incr.		
Age						
Age: 18-54 years	£11 991 [975]	0.099 [0.006]	-£1 773 [1 287]	0.004 [0.006]	0.092	0.93
Age: 54-72 years	£11 364 [918]	0.071 [0.021]	£1 135 [1 360]	0.009 [0.009]	-0.047	0.25
Age: > 72 years	£12 637 [1 013]	0.059 [0.014]	-£2 388 [1 316]	-0.002 [0.009]	0.117	0.96
Gender						
Female	£12 958 [984]	0.073 [0.011]	-£1 944 [1 315]	0.006 [0.005]	0.102	0.94
Male	£11 492 [651]	0.078 [0.010]	-£634 [885]	0.002 [0.005]	0.034	0.78
Mode of acquisition of infection						
Community acquired	£10 998 [640]	0.078 [0.011]	-£767 [869]	0.004 [0.004]	0.041	0.83
Nosocomial infection	£16 066 [1 665]	0.075 [0.012]	-£1 970 [2 373]	-0.006 [0.011]	0.094	0.78
Healthcare associated	£12 291 [1 317]	0.072 [0.011]	-£1 499 [1 764]	0.012 [0.012]	0.087	0.83
Charlson co-morbidity index score						
Score 0	£10 989 [924]	0.085 [0.011]	-£233 [1 312]	0.010 [0.009]	0.020	0.62
Score 1-2	£12 517 [909]	0.074 [0.010]	-£1 014 [1 213]	0.003 [0.007]	0.054	0.81
Score 3-4	£11 225 [1 215]	0.068 [0.013]	-£147 [1 880]	0.007 [0.013]	0.013	0.56
Score >5	£14 089 [1 700]	0.073 [0.015]	-£4 414 [2 084]	-0.013 [0.011]	0.209	0.98
BMI						
<18.5 kg/m^2	£17 016 [3 153]	0.071 [0.018]	-£6 471 [3 739]	0.003 [0.021]	0.322	0.97
18.5-24.9 kg/m^2	£11 179 [860]	0.070 [0.009]	-£1 072 [1 175]	0.012 [0.008]	0.066	0.87
25.0-29.9 kg/m^2	£11 826 [982]	0.075 [0.011]	£393 [1 414]	0.006 [0.007]	-0.015	0.42

30.0-39.9 kg/m^2	£12 723 [1 169]	0.086 [0.011]	-£2 378 [1 560]	-0.006 [0.008]	0.113	0.93
>=40 kg/m^2	£11 222 [2 098]	0.085 [0.021]	£1 645 [3 255]	-0.017 [0.019]	-0.099	0.27
Deep infection foci						
No	£9 855 [605]	0.073 [0.010]	£56 [850]	0.011 [0.005]	0.007	0.57
Yes	£16 111 [1 148]	0.081 [0.011]	-£3 479 [1 513]	-0.007 [0.005]	0.167	0.99
Endocarditis						
No	£11 703 [537]	0.076 [0.010]	-£1 153 [730]	0.003 [0.003]	0.060	0.95
Yes	£18 325 [4 080]	0.071 [0.016]	£1 654 [5 768]	0.022 [0.023]	-0.056	0.42
Methicillin resistance						
No	£11 805 [540]	0.077 [0.011]	-£984 [741]	0.004 [0.004]	0.053	0.92
Yes	£15 029 [3 083]	0.058 [0.028]	-£2 669 [3 780]	-0.009 [0.021]	0.127	0.75
Neutrophil count						
<6 10^9/L	£10 998 [640]	0.078 [0.011]	-£767 [869]	0.004 [0.004]	0.041	0.83
6-9 10^9/L	£12 824 [1 707]	0.087 [0.017]	-£1 404 [2 208]	-0.004 [0.011]	0.065	0.72
>9 10^9/L	£14 944 [1 793]	0.060 [0.010]	-£769 [2 513]	0.019 [0.010]	0.055	0.67
Coma						
No	£11 769 [558]	0.078 [0.010]	-£1 245 [751]	0.004 [0.004]	0.066	0.96
Yes	£13 945 [2 002]	0.058 [0.014]	£899 [2 975]	0.003 [0.015]	-0.043	0.39

* mean characteristics across the whole sample was used to estimate subgroup results; ** INHB: Incremental Net Health Benefit at £20,000 cost-effectiveness threshold; *** PCE Rifampicin: Probability that Rifampicin is cost-effective vs Placebo at £20,000 cost-effectiveness threshold

Discussion

The ARREST trial aimed to determine whether or not adjunctive rifampicin improved outcomes following *S. aureus* bacteraemia, but found no evidence of an effect either on resolution of bacteraemia or on mortality (design and effectiveness results of the trial are reported in detail in Chapters 3 and 4, respectively). In this chapter we first focused on evaluating the cost and HRQoL implications of *S. aureus* bacteraemia using the trial data.

This first set of analyses found that an episode of *S. aureus* bacteraemia costs, on average, £12 197 over 12 weeks (unadjusted results). The cost categories that contribute the most to costs (descriptive analyses) are length of stay (primary hospital admission and readmissions) and procedures undertaken in hospital. Determinants of higher episode costs (variables evaluated at baseline), evident from the trial population, were: whether the primary infection was nosocomial (episode costs 41% higher); deep focus primary infection (episode costs 43% higher); endocarditis (episode costs 65% higher), high neutrophil count (>9 10^9/L, episode costs 34% higher), and if the patient was comatose (episode costs 33% higher). For example, for an infection classified as having a *deep foci* the mean costs of the episode were estimated at £12 514, whilst for infections without a *deep focus* the mean costs were £8 752. In the ARREST population, neither age, gender, BMI, Charlson index nor methicillin resistance were found to determine costs at standard levels of standard statistical significance.

Analysis indicate that adjunctive rifampicin may save 10% of episode costs, although this result was not statistically significant at the standard 95% level (p=0.14). Descriptive, unadjusted, analyses suggest that these savings start in the first 14 days of treatment (unadjusted difference in the first 14 days was £413), but that are perhaps most relevant after 14 days (unadjusted difference of £787). Because the trial was not powered on this outcome, the relevance of this finding (had a larger sample size been recruited) is unclear. However, this result is consistent with the reduction in recurrences, which occurred in a small proportion of participants, but significantly fewer in the rifampicin group (1% vs 4% placebo).

As expected in this population of acutely ill patients, very low values of the EQ5D score were observed at baseline (mean EQ-5D score of 0.10). A high proportion of patients were comatose, and a high proportion of individuals had health states that the valuation algorithm ascribes as worse than death (i.e. returning negative EQ5D score values). Unadjusted figures show, however, that mean HRQoL score was significantly higher at 84 days (mean 0.30). The measure of benefit in the adjusted analysis considered QALYs over 84 days. QALYs are often the recommended measure of benefit for societal decision-makers, as they are generic and thus allow comparisons to be made across different treatments, conditions and patient populations. Give the high mortality and the low HRQoL that this population is subjected to, total QALYs over the 84 days were on average 0.077 per patient, only 33% of the maximum innings for this period (0.23 QALY or 84/365). Determinants of QALYs in the sample were: baseline EQ5D score (0.0064 QALYs lost for every 0.1 decrease in baseline EQ-5D); higher age (up to 0.044 QALY loss); Charlson index (up to 0.024 QALY loss) and comatose (mean QALY loss of 0.020). As opposed to total costs, deep foci infection did not affect total QALYs. After adjustment, the effect of rifampicin on total QALYs was positive (0.004 QALY) but not statistically significant (SE=0.004 QALY). Given the lack of statistical significance, the relevance of the finding that rifampicin has a positive (but small) effect on total QALYs is unclear; however, it is in accordance with the reduction in recurrences in the rifampicin group.

Public Health England conducts mandatory enhanced surveillance of MRSA bacteraemia since October 2005 and of MSSA bacteraemia since January 2011. From April 2017 to March 2017 823 cases of MRSA and 11 486 cases of MSSA were reported in England.[1] At the

episode cost determined in ARREST, these incidence figures imply a £150 million burden to the NHS.

Based on the analyses from ARREST, adjunctive rifampicin could result in 'cost' savings and negligibly small gains in mean QALYs. The cost-savings possibly arise from reductions in hospital stay and readmissions in the short term. In cost-effectiveness terms, adjunctive rifampicin could be said to dominate placebo. Our within-trial economic analysis, however, excluded potentially important outcomes, such as resistance arising from increased use of rifampicin and the clinical consequences of its drug-drug interactions (which may not have been captured fully in our analyses as costs of non-antibiotic drugs were not included, nor were costs of monitoring tests, e.g. for toxicity). This was a pragmatic decision because patients enrolled in this trial had wide range of underlying conditions and will have required a very large number of other drugs. A decision was therefore made not to try record all these other drugs on CRFs, making them impossible to cost. Similarly it was difficult to know what quantitative data to record to assess drug interactions – rather than collect a large amount of free text to try to code, and risk missing different items for different episodes, a pragmatic decision was made to not include these on CRFs either. Moreover, the ARREST trial was conducted under experimental conditions and, despite providing unbiased estimates of treatment effects, practice may not be as homogeneous and hence further research could confirm whether any predicted cost-savings would be effectively realised in practice.

Chapter 6 Discussion

We conducted a large, multi-centre, pragmatic, placebo-controlled trial which randomised 758 adults with *S. aureus* bacteraemia. Our trial was designed to determine whether rifampicin, added to standard 'backbone' antibiotics for up to 14 days, reduced bacteriologically-confirmed failure or recurrence or death by 12-weeks. We found no evidence that rifampicin affected any of the composite primary or secondary efficacy measures including mortality, the duration of bacteraemia, or the development of rifampicin-resistant *S. aureus.* Rifampicin was, however, associated with a small but significant reduction in bacteriologically and clinically-defined disease recurrences.

The population included in the trial represents the severity and heterogeneity of *S. aureus* bacteraemia. Participants were mostly older adults (median age 65 years), many with a number of co-morbidities (median Charlson score 2). A substantial minority (9.2%) were enrolled in an intensive care unit, reflecting the severity of the infection. Substantial improvements in hospital infection prevention and control over the last decade in the UK meant that most (64.0%) infections were acquired in the community, with only 17.4% being nosocomial in origin (acquired more than 48 hours after hospital admission). Similarly, the UK has witnessed a major decline in MRSA infections over the same period and only 6.2% of patients had bacteraemia caused by MRSA.[63] A deep infection focus, denoting a complicated infection, was present at baseline in 301 (39.7%), around half with endocarditis, orthopaedic or intravascular devices, or osteoarticular infections, and 139 (18.3%) had no established infection focus. Therefore a substantial proportion of patients had what are generally as considered as uncomplicated infections, in which there is a single, superficial, and easily removable infection focus (an infected intravascular catheter, for example) without evidence of deep infection foci.

One of the key findings from the trial is the enormous variation in the choice and duration of 'backbone' antibiotics (**Table 26** in **Appendix 2**). The majority (81.7%), however, received flucloxacillin (an anti-staphylococcal penicillin) at some point in their primary treatment. In the United Kingdom and Australia, flucloxacillin is the recommended first-line anti-staphylococcal penicillin for MSSA infections; whereas other agents, such as nafcillin and cloxacillin, are recommended in the United States. There is no evidence supporting clinically

relevant differential anti-staphylococcal activity between these antibiotics,[64,65] and we therefore believe our results are generalisable across countries regardless of their chosen anti-staphylococcal penicillin. 50.1% of patients received a glycopeptide at some point in their primary treatment, likely reflecting ongoing concerns about MRSA infections despite the overall low rates, particularly given the severity of disease in many of the trial participants. The use of other antibiotics (including open-label rifampicin) and the total duration of active antibiotic therapy (median 29 days) were similar between randomised groups. Fewer rifampicin than placebo treated participants were restarted on antibiotics after the primary treatment course, which may reflect the lower recurrence rate in the placebo group. The variety of antibiotics received demonstrates the utter infeasibility of conducting a trial restricting to one single backbone antibiotic. Further, had we used only one standard antibiotic regimen, clinicians could legitimately argue that the effect of rifampicin might be different on another backbone antibiotic. All antibiotic regimens were chosen by infection specialists taking into account individual patient allergy and concomitant medication. We found no evidence of variation in the lack of effect of rifampicin by initial treatment class. We therefore consider that the results are more generalizable than would have been obtained from one single regimen.

Planned subgroup analysis did not identify a sub-population of participants who clearly benefited from the addition of rifampicin. There was a suggestion that rifampicin's effect may have varied according to antibiotics used at randomisation, with any benefit restricted to those with MSSA infection treated with flucloxacillin alone. However, this result has uncertain clinical significance. There was no evidence of benefit if flucloxacillin was used with vancomycin or another antibiotic, or if antibiotic class was used to define subgroups, findings that are inconsistent with an isolated effect of flucloxacillin. With 20 subgroups analysed, one statistically significant association may have occurred by chance. Many infection specialists might have predicted that rifampicin might benefit those with deep, complicated infection the most, and possibly those with disease caused by MRSA. We could find no such associations, although only a small minority of participants had MRSA bacteraemia. Indeed, if anything those with MRSA bacteraemia did worse with rifampicin than placebo (**Figure 5(b)**).

We hypothesised that the early addition of rifampicin to standard antibiotic treatment would enhance the early killing of *S. aureus* and thereby improve outcomes. The trial inclusion criteria therefore required rifampicin to be initiated anywhere from 0-96 hours after initiating

active antibiotics for the infection. Given most patients with *S. aureus* bacteraemia are very unwell and require immediate empirical antibiotic therapy, and it takes at least 36 hours to culture and identify *S. aureus* from blood cultures, it is unsurprising that participants received a median of 62 hours of other active antibiotics before treatment with rifampicin. This may have represented a clinically meaningful delay in initiating rifampicin treatment which could have affected efficacy. However, there was no evidence of such an effect considering time from randomisation to initiation of rifampicin/placebo as either categorical subgroups or as a continuous interaction factor (**Figure 5(b)**). Additional sub-group analysis needs to be interpreted carefully, given the number of tests performed[66] and we do not believe they should be highlighted as clinically significant findings within the conclusions of the study.

We believe that the study results refute the hypothesis that adjunctive rifampicin enhances *S. aureus* killing in blood and thereby reduces the risk of dissemination and death.[15] Both randomised groups had similar rates of bacterial clearance in blood, and there was no evidence of difference in all-cause mortality over the short (2 weeks), medium (12 weeks) or even in the longer-term (>52 weeks). Even the 50% of deaths that were adjudicated as definitely/probably due to *S. aureus* (50%) occurred similarly in rifampicin and placebo groups. However, the observed mortality in our trial was lower than that observed in many recent observational studies. For example, a recent large multi-centre case-series reported substantially higher 12-week mortality (29.2%)[67] than we observed (14.8%). The few randomised controlled trials that have been reported in this disease (the trial of daptomycin in *S. aureus* bacteraemia,[68] for example) tend to report lower mortality. This probably reflects differences in the populations between observational and interventional studies. It is possible that the most severely unwell patients, who are expected to die quickly, are less likely to enter interventional studies. Indeed, in ARREST there were 129 patients who either died or were considered too unwell for active treatment and therefore did not join the trial (**Figure 2**). Mortality would have nearly doubled had they joined the trial and died. But there may be other reasons for the lower mortality observed in the ARREST trial. Regular infection specialist consults were also mandatory for the trial, which may have reduced mortality. Infection consults have been associated with improved *S. aureus* bacteraemia outcomes in observational studies.[69]

Another hypothesis, that rifampicin enhances the sterilisation of deep infection foci and thus reduces disease recurrences, is, at least partially, supported by our findings.[70] We found a

small but statistically significant reduction in recurrences in the rifampicin group, suggesting some biological activity of the drug. However, the clinical significance of such a small reduction is unclear. The numbers-needed-to-treat to prevent bacteriologically and clinically-defined recurrences were 29 and 26 respectively. More importantly, prevention of recurrences did not affect either short-term or long-term mortality (**Figure 9, Figure 10**). Of note, the independent, blinded endpoint review committee adjudicated that recurrences were much more likely to have been caused by failure to recognise or remove the primary infection focus than by failure antibiotic treatment (**Table 7**). This observation demonstrates the importance of source management in future research to improve outcomes from *S. aureus* bacteraemia. Recent strategies that enhance the identification of infection foci by positron emission tomography (PET) scanning have been associated with reduced mortality from *S. aureus* bacteraemia.[71] Taken together, these findings suggest the need for a multifaceted approach to improving outcomes from *S. aureus* bacteraemia. Rifampicin may assist in sterilising deep *S. aureus* infection foci and prevent a few recurrences, but it does not replace the need to define and, when possible, drain or remove the infection focus.

The modest benefit of rifampicin on recurrences (and any resulting cost savings) needs to be balanced against the toxicity of rifampicin and complications surrounding its use, especially in an older population with co-morbidities, often requiring other drug treatments. Predicted drug interactions or pre-existing liver disease prevented 306/2896 (10.6%) screened subjects from being randomised. Whilst there was no evidence of differences between groups in the proportions with SAEs, significantly more antibiotic-modifying AEs and drug-interactions occurred in rifampicin participants. AEs were predominantly gastrointestinal disorders and, interestingly, renal impairment. Rifampicin was associated with acute kidney injury in 17 participants, compared with 6 placebo participants. Although the numbers are small, and renal impairment is a recognised toxicity of rifampicin in the Summary of Product Characteristics, this is an important aspect of its use which is rarely considered by clinicians. In contrast, drug-induced liver injury was predicted to be common but turned out to be extremely rare, possibly because patients vulnerable to liver injury were not enrolled.

The strengths of the ARREST trial include its placebo-controlled, multi-centre and pragmatic design. This ensures it provides generalisable, clinically relevant findings to clinicians and patients within the NHS. It is also the largest trial ever conducted examining *S. aureus* bacteraemia treatment. It does, however, have important limitations that reflect the many

challenges of performing trials in acutely unwell patients with severe bacterial infections and in the current UK trial funding arena.[72] The heterogeneous nature of this severe disease, and the requirement to randomise patients within 96 hours of the start of antibiotic therapy because of the underlying hypothesis, led to a large number of ineligible patients and meant recruitment was slower than anticipated. Only 26.6% (770/2896) of those screened were enrolled; the most common reason was having already received >96 hours of antibiotics, in around one-third of those not enrolled (664 (31.2%). Furthermore, 232 (10.9%) screened subjects were not randomised because rifampicin was considered mandatory. This information was available only as a reason for ineligibility with no additional details, but anecdotally prosthetic device-related infections were common in these patients. Rifampicin's clinical effect may potentially have been reduced as a consequence of excluding these patients, reducing the findings' relevance to those with bacteraemia associated with infected prostheses, where rifampicin may have more benefit.[33]

A proportion of patients initiated open-label rifampicin or stopped blinded trial drug early, predominantly for drug-drug interactions or AEs. Such deviation from intended treatment would be expected in normal clinical practice, and therefore the intention-to-treat comparison of the groups likely reflects the effectiveness of rifampicin more widely. There was however also no evidence of benefit from rifampicin in the per-protocol population who received ≥80% of expected doses. Outcome ascertainment was very high, with only a small number (~9%) of patients in whom vital status and/or signs and symptoms could not be ascertained at the 12 week follow-up visit. The total number randomised in error and lost-to-follow-up or withdrawing consent was very close to the 10% incorporated in the sample size calculation.

A far more critical limitation to timely completion of this trial was the heterogeneity in the trials support network in the UK, which is far more suited to recruiting large numbers of chronically unwell individuals from a small number of fixed clinics, than recruiting acutely unwell individuals who present sporadically at varying times of day and night and require a great deal of care in explaining research at a time of acute illness. Some centres received excellent support and were able to recruit larger numbers. Others received, for example, research nurse support on two fixed days of the week, regardless of when patients presented acutely unwell, or were unable to access promised support when patients did present, because research staff were committed to fixed clinics at the time. Thus in many centres the burden of recruiting patients and conducting research visits fell to the PI, typically a consultant

microbiologist or infection specialist who took this on outside their day-to-day work. There are clearly enormous challenges for research networks in supporting trials in acute, relatively uncommon, sporadic, diseases – but their severity, with one in six patients dying in this trial - highlights the importance of finding a way to do this. Even more frustrating was the system of "targets", which are extremely difficult to assess in acute illnesses such as *S. aureus* bacteraemia. One of the top recruiting sites was forced to close to recruitment early, despite the trial struggling as a whole to meet its recruitment targets, because their individual site target had been met and the local research office was required to move its resources to other studies to avoid being penalised. The unintended consequences of rigid adherence to targets, which are really impossible to specify with any degree of confidence in acutely presenting complaints such as *S. aureus* bacteraemia, was an increase in the total time the trial took to recruit. Particularly when randomised controlled trials are competing with observational studies for research support, there needs to be a better way to encourage sites that are able to recruit to trials to do so beyond arbitrary targets.

Originally, the trial was powered to detect an absolute difference of 10% in bacteriological failure/recurrence or death from 35% to 25% **and** a 7% absolute reduction in mortality from 16% to 9%, based on results from a small systematic review.[73] Slow recruitment meant that the mortality co-primary endpoint was moved to a secondary endpoint, consequently reducing the sample size needed to detect the 10% absolute reduction in bacteriological failure/recurrence or death because the two-sided alpha (false positive) increased from 0.025 (two co-primary outcomes) to 0.05 (one primary outcome). The 758 eligible participants included are more than double the number in the largest previous trial in *S. aureus* bacteraemia,[24] and increase the total numbers with *S. aureus* bacteraemia recruited in randomised trials over the last 50 years by 50%. The 95% CI around our estimates of the difference between rifampicin and placebo lie within 7.5%, smaller than the 10% non-inferiority margins recommended by licencing authorities for antibiotic trials and commonly used in other infections such as HIV. This would have been considered to conclusively demonstrate non-inferiority of rifampicin had we used an active comparator. Although the trial was designed to test the superiority of rifampicin, it thus provides convincing evidence of non-inferiority of rifampicin to placebo; that is, convincing evidence of lack of benefit. A small minority (13%) used open-label rifampicin in the placebo group, but per-protocol analyses confirmed this well-estimated lack of benefit of rifampicin over placebo.

We found that an episode of *S. aureus* bacteraemia costs, on average, £12 197 over 12 weeks. These costs were driven primarily by length of stay and procedures undertaken in hospital. Last year (April 2016 to March 2017) there were 12 309 episodes of *S. aureus* bacteraemia reported within the NHS in England.[74] We therefore estimate *S. aureus* costs the NHS around £150 million each year.

Interventions that reduced these costs would be welcome. On the basis of the clinical data provided by the trial we concluded that rifampicin was of no overall clinical benefit to individuals with *S. aureus* bacteraemia. However, our cost effectiveness analysis suggested adjunctive rifampicin may have a possible health economic benefit to the NHS. Rifampicin was estimated to save 10% of episode costs (p=0.14). Most of these savings related to small reductions in length of hospital stay, especially after the first 14 days of treatment. These reductions probably relate to the small but significant reductions on recurrences associated with the use of rifampicin over placebo (1% vs 4%; p=0.01).

Important limitations to the cost-effectiveness analysis include the missing costs of rifampicin toxicity (including monitoring for toxicity) and drug-drug interactions in the analysis. These important clinical complications of rifampicin treatment were highlighted in the clinical data but were not captured in the cost effectiveness analysis. In addition, the widespread use of rifampicin would undoubtedly lead to the increased prevalence of rifampicin resistance amongst *S. aureus* and other medically important bacteria. These costs could be substantial, especially if it caused a rise in rifampicin-resistant *Mycobacterium tuberculosis* infections, and have not been considered. In short, on balance, we do not believe that the possible cost savings of rifampicin to the NHS should outweigh the lack of overall clinical benefit to an individual with *S. aureus* bacteraemia. In support of this position is the lack of a significant effect of rifampicin on QALYs.

The ARREST trial was developed with the assistance of the Healthcare-associated Infection Service Users Research Forum and Jennifer Bostock, our PPI representative. Ms Bostock advised on the inclusion of incapacitated adults and the application of the Mental Capacity Act, and the information provided to patients. The information sheets, consent forms and recruitment processes were developed in collaboration with the SURF and Ms Bostock to help ensure that they communicated the risks and benefits clearly and appropriately. There were sensitive ethical issues which arose at ethical review and the PPI representative was

instrumental in helping the team gain ethical approval. Furthermore, when it was necessary for the trial team to request an extension to the study from the funders Ms Bostock accompanied them to the meeting and helped put the case as to why the trial was important to patients/relatives and the public. The panel remarked that it was the first time they had seen a public member attend such a meeting. It reflected the trial team's commitment to PPI and the creative use to which they engaged the 'expertise' of Ms Bostock. Ms Bostock was also a member of the ARREST Trial Steering Committee.

It was Ms Bostock's idea to run a qualitative sub-study within the main trial (see Chapter 4). The study was designed, developed and delivered by her with assistance from the trial team. It was deemed important that the PPI representative was responsible for this aspect of the trial as it was felt that there would be a better response rate and more honest answers if the person conducting the study was independent and had a 'public voice'. The sub-study was small in scope and had limited findings; however it was an unusual inclusion in a trial of this nature.

PPI played, and will continue to play, an active role in disseminating the trial's results. Ms Bostock has both reviewed and co-authored some of the main academic outputs from the study and the main conference presentations of the results, as well as a leaflet presenting results to patients and their GPs (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1010425/#/). It is important to the entire trial team that dissemination goes beyond the traditional academic and healthcare professional communities to others, patient groups and the wider public. With this in mind the team agreed that having a creative approach to dissemination to engage with patients, the public and policy makers may benefit this process. An example of this creative approach is provided by an Infographic, designed by Will Everett (Science Communications Officer at the MRC CTU at UCL), which summarises the trial's findings for dissemination (**Figure 21**). This was reviewed and revised by the PPI advisor and will be used to showcase the trial and results to patients and the public after publication. In addition, Ms Bostock and other members of the trial team were interviewed for a PodCast aimed at clinicians (please go to: https://soundcloud.com/user-110325996-105034477/arrest-podcast-v03/s-J4lta). The interviewees discussed the results of the study and their implications for healthcare workers and patients and the public. Ms Bostock and her wider network will continue to disseminate the results of the study to relevant audiences via her links with MRSA Action UK, The Healthcare Infection Society, The Infection Prevention Society, The Patients Association, The

Research Design Service PPI Advisory Group and The Biomedical Research Centre (GSTT) PPI Advisory Group.

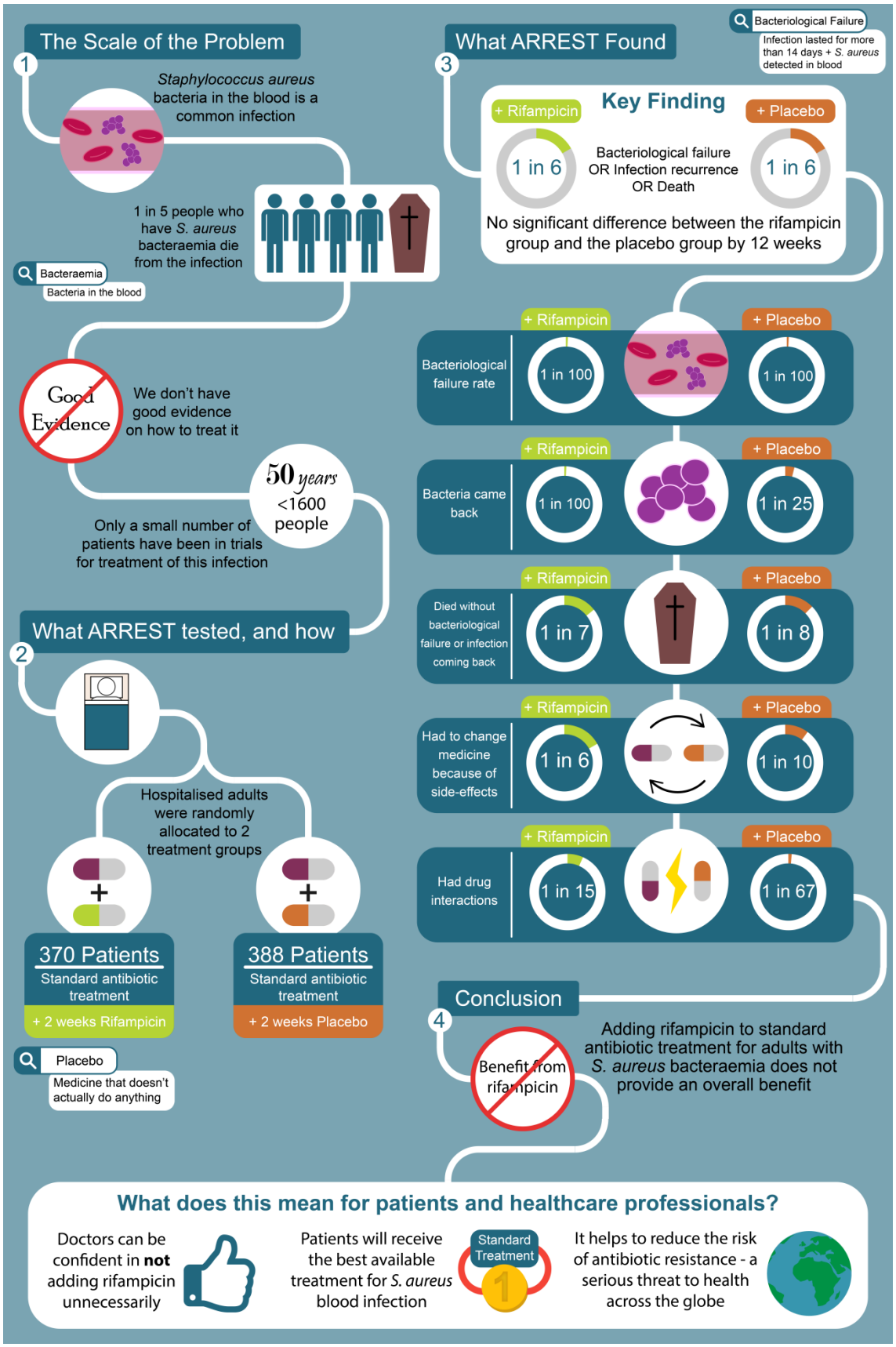


Figure 21 ARREST infographic

From Ms Bostock's perspective the trial has succeeded in involving patients and the public in a way that is rare in clinical trials of medicines. The team's support, patience and willingness to adapt and change the trial in response to public input have benefited both the public representative and also the trial. Being involved in the trial has enabled Ms Bostock to develop skills and understanding of clinical trials and PPI which she will use to benefit other research and it is hoped that researchers conducting similar trials will adopted some of the methods used in ARREST as a model of good PPI practice.

Summary and future research

In summary, the ARREST trial provides high quality data where there are almost none. The clinical management of infectious diseases and, in particular, the treatment of many common severe bacterial infections, lacks high quality clinical trial evidence. The situation is especially stark for *S. aureus* bacteraemia, probably the commonest, life-threatening, community and hospital-acquired infection worldwide. But whilst the ARREST trial addresses some of these inadequacies, it also leaves many questions unanswered as to how to improve outcomes from *S. aureus* bacteraemia.

The ARREST trial has exposed two possible windows in which to intervene. The first is in the acute phase, when *S. aureus* can be cultured from the bloodstream and a severe inflammatory response (or 'sepsis') can have rapidly fatal consequences. The interventions in this early phase are those targeted at more rapid recognition or diagnosis of *S. aureus* bacteraemia, and those which might enhance bacterial killing and control the detrimental effects of the inflammatory response. Future research therefore might investigate novel molecular techniques, perhaps based on rapid next-generation sequencing, to identify *S. aureus* from the blood and predict drug susceptibility such that effective antibiotic treatment can be given quickly. The question of whether intensified antibiotic therapy - be it different drugs, doses, or drug combinations - might speed bloodstream sterilisation very early in the infection and thereby improve outcomes has not been resolved by ARREST; although it has delineated the considerable challenges of conducting a trial to address this question. Likewise, early control of the inflammatory response, using corticosteroids or newer drugs targeted at specific molecules in the inflammatory cascade, might reduce early mortality and would be amenable to testing by clinical trials.

However, given the challenges we experienced conducting this trial, this is probably not the more important priority for future studies. Rather, the second interventional window in *S. aureus* bacteraemia is more easily accessible to trialists than the first window and, as our health economic analysis suggests, may also bring substantial cost savings. It opens after around 72-96 hours of active antibiotic treatment, once the acute phase is over, and concerns interventions to prevent, detect and manage the longer-term complications of the *S. aureus* bacteraemia, including disease recurrence. These complications include endocarditis, vertebral osteomyelitis, and other deep and potentially occult infection foci. As recent PET scan studies have shown,[71] perhaps the most promising strategies which should be prioritised for future research are those which aim to speed the detection of these complications and improve their antibiotic and surgical management; these could have major impacts on outcome and costs. A clinical trial investigating these strategies against current standards of care would be both feasible and likely to have a major impact upon clinical practice.

Chapter 7 Conclusions

Adjunctive rifampicin did not improve outcomes from *S. aureus* bacteraemia, with the exception of a modest reduction in disease recurrence which may be associated with reduced costs. Given the clinical effect had no impact on short-term or longer-term mortality, rifampicin significantly complicated other drug treatment, and widespread rifampicin use risks increasing resistance amongst *S. aureus* and other bacteria (for example, *Mycobacterium tuberculosis*), we consider that despite potential cost savings adjunctive rifampicin provides no overall benefit over standard antibiotic therapy in adults with *S. aureus* bacteraemia.

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Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

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