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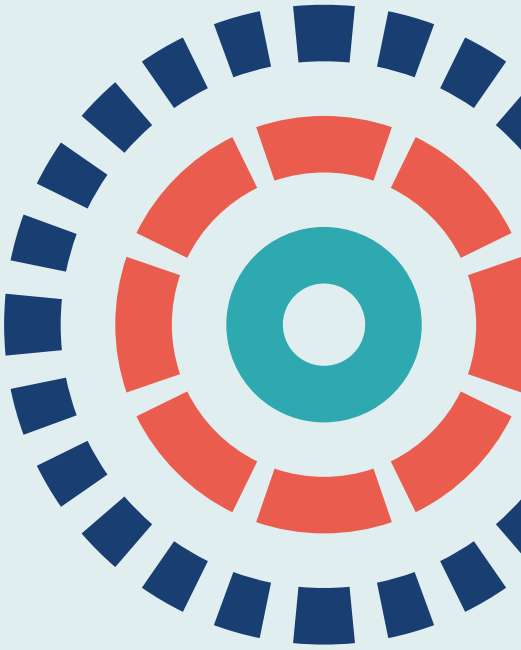
Health Technology Assessment

Volume 23 • Issue 38 • August 2019

ISSN 1366-5278

Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT

Matthew Scarborough, Ho Kwong Li, Ines Rombach, Rhea Zambellas, A Sarah Walker, Martin McNally, Bridget Atkins, Michelle Kümin, Benjamin A Lipsky, Harriet Hughes, Deepa Bose, Simon Warren, Damien Mack, Jonathan Folb, Elinor Moore, Neil Jenkins, Susan Hopkins, R Andrew Seaton, Carolyn Hemsley, Jonathan Sandoe, Ila Aggarwal, Simon Ellis, Rebecca Sutherland, Claudia Geue, Nicola McMeekin, Claire Scarborough, John Paul, Graham Cooke, Jennifer Bostock, Elham Khatamzas, Nick Wong, Andrew Brent, Jose Lomas, Philippa Matthews, Tri Wangrangsimakul, Roger Gundle, Mark Rogers, Adrian Taylor, Guy E Thwaites and Philip Bejon on behalf of the OVIVA study



DOI 10.3310/hta23380

Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT

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Declared competing interests of authors: Adrian Taylor reports personal fees from Zimmer Inc., Corin Group and DePuy Synthes Companies outside the submitted work. Martin McNally reports personal fees from Bonesupport AB outside the submitted work. R Andrew Seaton reports personal fees from previous consultancy and funding for speaking at educational meetings (Novartis Pharma) and consultancy for Merck Sharp & Dohme Corp. (MSD) outside the submitted work. Harriet Hughes reports other competing interests from Gilead Sciences Inc., MSD, Biocomposites, and personal fees from Biocomposites and Cubist Pharmaceuticals outside the submitted work. Jennifer Bostock was a member of the Health Services and Delivery Research Commissioned Panel Members during this project.

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published August 2019
DOI: 10.3310/hta23380

This report should be referenced as follows:

Scarborough M, Li HK, Rombach I, Zambellas R, Walker AS, McNally M, *et al*. Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT. *Health Technol Assess* 2019;**23**(38).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/36/29. The contractual start date was in March 2013. The draft report began editorial review in May 2016 and was accepted for publication in December 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT

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Background: Management of bone and joint infection commonly includes 4–6 weeks of intravenous (IV) antibiotics, but there is little evidence to suggest that oral (PO) therapy results in worse outcomes.

Objective: To determine whether or not PO antibiotics are non-inferior to IV antibiotics in treating bone and joint infection.

Design: Parallel-group, randomised (1 : 1), open-label, non-inferiority trial. The non-inferiority margin was 7.5%.

Setting: Twenty-six NHS hospitals.

Participants: Adults with a clinical diagnosis of bone, joint or orthopaedic metalware-associated infection who would ordinarily receive at least 6 weeks of antibiotics, and who had received ≤ 7 days of IV therapy from definitive surgery (or start of planned curative treatment in patients managed non-operatively).

Interventions: Participants were centrally computer-randomised to PO or IV antibiotics to complete the first 6 weeks of therapy. Follow-on PO therapy was permitted in either arm.

Main outcome measure: The primary outcome was the proportion of participants experiencing treatment failure within 1 year. An associated cost-effectiveness evaluation assessed health resource use and quality-of-life data.

Results: Out of 1054 participants (527 in each arm), end-point data were available for 1015 (96.30%) participants. Treatment failure was identified in 141 out of 1015 (13.89%) participants: 74 out of 506 (14.62%) and 67 out of 509 (13.16%) of those participants randomised to IV and PO therapy, respectively. In the intention-to-treat analysis, using multiple imputation to include all participants, the imputed risk difference between PO and IV therapy for definitive treatment failure was –1.38% (90% confidence interval –4.94% to 2.19%), thus meeting the non-inferiority criterion. A complete-case analysis, a per-protocol analysis and sensitivity analyses for missing data each confirmed this result. With the exception of IV catheter complications [49/523 (9.37%) in the IV arm vs. 5/523 (0.96%) in the PO arm)], there was no significant difference between the two arms in the incidence of serious adverse events. PO therapy was highly cost-effective, yielding a saving of £2740 per patient without any significant difference in quality-adjusted life-years between the two arms of the trial.

Limitations: The OVIVA (Oral Versus IntraVenous Antibiotics) trial was an open-label trial, but bias was limited by assessing all potential end points by a blinded adjudication committee. The population was heterogenous, which facilitated generalisability but limited the statistical power of subgroup analyses. Participants were only followed up for 1 year so differences in late recurrence cannot be excluded.

Conclusions: PO antibiotic therapy is non-inferior to IV therapy when used during the first 6 weeks in the treatment for bone and joint infection, as assessed by definitive treatment failure within 1 year of randomisation. These findings challenge the current standard of care and provide an opportunity to realise significant benefits for patients, antimicrobial stewardship and the health economy.

Future work: Further work is required to define the optimal total duration of therapy for bone and joint infection in the context of specific surgical interventions. Currently, wide variation in clinical practice suggests significant redundancy that likely contributes to the excess and unnecessary use of antibiotics.

Trial registration: Current Controlled Trials ISRCTN91566927.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 23, No. 38. See the NIHR Journals Library website for further project information.

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List of abbreviations

BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTU	clinical trials unit
CUA	cost–utility analysis
DAIR	debridement, antibiotics and implant retention
DMC	Data Monitoring Committee
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
GP	general practitioner
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
IV	intravenous
MEMS	Medication Event Monitoring System
MITT	modified intention-to-treat analysis
NICE	National Institute for Health and Care Excellence
OHS	Oxford Hip Score
OKS	Oxford Knee Score
OPAT	outpatient parenteral antimicrobial therapy
OVIVA	Oral Versus IntraVenous Antibiotics
PIS	patient information sheet
PO	oral
PP	per protocol
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SmPC	summary of product characteristics
VAS	visual analogue scale

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Plain English summary

Treatment of bone and joint infection usually requires a long course of antibiotics. Doctors usually give these by injection through a vein (intravenously) for the first 4–6 weeks, rather than by mouth (orally). Although intravenous (IV) administration is more expensive and less convenient for patients, most doctors believe that it is more effective. However, there is little evidence to support this. The OVIVA (Oral Versus IntraVenous Antibiotics) trial set out to challenge this assumption.

A total of 1054 patients from 26 UK hospitals were randomly allocated to receive the first 6 weeks of antibiotic therapy either intravenously or orally. Irrespective of the route of administration, the choice of antibiotic was left to an infection specialist so as to ensure that the most appropriate antibiotics were given. Patients were followed up for 1 year.

Thirty-nine participants were lost to follow-up. Among the remaining 1015 participants, treatment failure occurred in 14.6% of those treated intravenously and 13.2% of those treated with PO antibiotics. This difference could easily have occurred by chance. Even if it was not by chance, the difference does not suggest that PO therapy is associated with worse outcomes than IV therapy and is too small to conclude that PO therapy is better than IV therapy.

Participants in the IV group stayed in hospital longer and 10% of them had complications related to the IV line used for administering the antibiotics. In addition, their treatment was, overall, more expensive.

We conclude that PO antibiotic therapy has no disadvantages for the early management of bone and joint infection. It is also cheaper and associated with fewer complications.

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Scientific summary

Background

Bone and joint infection in adults causes considerable morbidity. Treatment costs are estimated at £20,000–40,000 per patient. The current standard of care in most UK centres includes a prolonged course (i.e. 4–6 weeks) of intravenous (IV) antibiotics during the early treatment phase, although there is no evidence that PO antibiotic therapy results in worse outcomes.

Objectives

The primary objective of the OVIVA (Oral Versus IntraVenous Antibiotics) trial was to determine whether or not oral (PO) antibiotic therapy is non-inferior to IV therapy when given for the first 6 weeks of treatment for bone and joint infection, as judged by the proportion of patients experiencing definite treatment failure during 1 year of follow-up.

Secondary objectives included assessment of:

1. serious adverse events (SAEs), including death (i.e. all cause) according to treatment allocation
2. IV catheter line complications (i.e. infection, thrombosis or other events requiring early removal of the line)
3. *Clostridium difficile*-associated diarrhoea
4. 'probable' and 'possible' treatment failure as composites with definitive treatment failure
5. early termination of the planned 6-week period of PO or IV antibiotics
6. resource allocation using (1) length of hospital stay, (2) outpatient visits and (3) antibiotic costs
7. quality of life, as evaluated by EuroQol-5 Dimensions questionnaire
8. Oxford Hip and Knee Scores (when infection involved the hip or knee)
9. patient adherence to treatment, as indicated by a Medication Event Monitoring System (MEMS) in a subset of participants.

Methods

The trial was a multicentre, open-label, parallel-group, randomised (1 : 1), non-inferiority study. The primary end point was definite treatment failure within 1 year. Eligible patients had anticipated life expectancy of > 1 year, had a bone and joint infection for which at least 6 weeks of antibiotic therapy was considered necessary and had received ≤ 7 days of IV antibiotic therapy following surgery (or from the start date of planned curative therapy if there was no planned surgical intervention). Exclusion criteria were recent *Staphylococcus aureus* bacteraemia, bacterial endocarditis or other infection mandating a prolonged course of IV antibiotic therapy. Data were collected manually from care records, direct patient contact and questionnaires prior to entry onto a centralised database (OpenClinica Enterprise version 3.4, 2014; Waltham, MA, USA). The occurrence of definitive treatment failure was adjudicated by a blinded end-point committee that reviewed relevant clinical records, redacted for indicators of treatment allocation and patient identifiers.

Data were analysed using Stata® (version 14SE, StataCorp LP, College Station, TX, USA). The non-inferiority margin was set at 7.5% [i.e. an absolute upper two-sided 90% confidence interval (CI) around the unadjusted difference between PO and IV therapy of $\leq 7.5\%$ was considered non-inferior].

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Results

A total of 1054 participants from 26 UK centres (including 228 from a single-site internal pilot study) were randomised. Participants were evenly matched between the two arms of the trial for age, clinical presentation, comorbidities, site and type of surgery, organism and histopathological diagnosis. Primary end-point data were available for 1015 (96%) participants.

Definitive treatment failures were observed in 74 out of 527 (14.04%) participants in the IV arm and 67 out of 527 (12.71%) participants in the PO arm. A total of 432 (81.97%) and 442 (83.87%) participants in the IV and PO arms, respectively, did not experience definitive treatment failures over the 1-year follow-up. Data on treatment failures were missing for 21 (3.98%) participants in the IV arm and 18 (3.42%) participants in the PO arm.

In an intention-to-treat analysis, using multiple imputation to include all randomised participants, the imputed risk difference (PO – IV) for definitive treatment failure was estimated to be –1.38% (90% CI –4.94% to 2.19%).

In a complete-case analysis, which included only those participants with primary end-point data at 1-year follow-up, 74 out of 506 (14.62%) and 67 out of 509 (13.16%) participants in the IV and PO arms of the trial, respectively, suffered a definitive treatment failure, representing a risk difference (PO – IV) of –1.46% (90% CI –5.03% to 2.11%).

A per-protocol analysis, which included 909 patients who followed their allocated treatment strategy for at least 4 weeks, showed definitive treatment failure in 69 out of 443 (15.58%) participants in the IV arm and 61 out of 466 (13.09%) in the PO arm of the trial, representing a risk difference of –2.49% (90% CI –6.31% to 1.34%).

All end-point analyses, as well as sensitivity analyses to investigate the potential impact of missing data, were consistent in showing that the non-inferiority criteria were met.

Time to event modelling showed no difference in the time to definitive treatment failure between the arms.

Prespecified subgroup analyses according to recruiting centre, pathogen and surgical management (e.g. retention or removal of metalware) showed no significant difference in rate of definitive failure between the two arms of the trial.

With the exception of line complications [49/523 (9.37%) in the IV arm vs. 5/523 (0.96%) in the PO arm], there was no significant difference between the two arms of the trial in the incidence of SAEs, including death.

Participants randomised to IV therapy were hospitalised for longer than those randomised to PO therapy, with a median (interquartile range) inpatient stay of 14 (11–21) days and 11 (8–20) days, respectively. Patients randomised to IV therapy had an unadjusted excess treatment cost of £2727 (95% CI £1437 to £3980) through to 1 year of follow-up.

Implications

1. Clinical outcome. The OVIVA trial demonstrates no clinical advantage of using prolonged IV therapy compared with PO therapy in the early treatment of bone and joint infections requiring $\geq$ 6 weeks of antibiotic therapy. The findings directly challenge a widely held view that the management of bone and joint infection mandates a prolonged course of IV antibiotic therapy. This dogma was most notably published as a specialist opinion in 1970, and since then it had been perpetuated through several

iterations of guidelines, protocols and textbooks. A number of smaller studies investigating the effectiveness of PO antibiotic therapy in osteomyelitis, including a meta-analysis involving 180 patients, have suggested similar results but none was large enough to influence management. We believe that the findings of the OVIVA study provide sufficiently robust evidence to inform a widespread change in clinical practice.
2. Safety. Use of PO antibiotic therapy mitigates the risks associated with long-term IV access. In our trial, around 10% of participants randomised to IV therapy developed complications directly related to the use of IV lines.
3. Cost. In addition to the clinical findings, the results demonstrate that PO antibiotic therapy provides a significant cost benefit and cost-effectiveness advantage over IV therapy, without additional risk of adverse events. Assuming a total of 9000 bone and joint infections in adults are managed in UK secondary care per year, routine use of PO as opposed to IV therapy could save the NHS around £25M per year.
4. Patient pathway. Compared with IV therapy, PO antibiotics allow for earlier discharge from hospital. This is of considerable advantage to patients and the NHS. It provides patient satisfaction, contributes to the cost savings, optimises inpatient flow and limits the risks of health-care associated infections. Although not formally assessed during the study, our experience suggests that use of PO therapy is widely perceived as more convenient for patients. Most patients on prolonged IV therapy require regular attendance of health-care providers and often are restricted in their social and professional activities by the IV access device.
5. Antibiotic stewardship. The current availability of a wide range of effective PO antibiotics allows clinicians to select the most appropriate, narrow-spectrum agent. This directly supports a national objective of protecting the most valuable IV antibiotic agents against emergence of resistance by minimising the use of unnecessarily broad-spectrum IV antibiotics.

Conclusion

Oral antibiotics are a safe, effective and convenient alternative to IV therapy in the early management of serious bone and joint infection. Translation of these findings into routine clinical practice is likely to benefit patients and provides an opportunity for substantial cost savings to the NHS.

Future research

1. Duration of therapy. To further support patient safety, cost improvement and antimicrobial stewardship, additional work to define the optimal total duration of antibiotic therapy in bone and joint infection is necessary. Currently, there is considerable variation between centres and between clinicians, which suggests that there may be significant redundancy in antibiotic use. This almost certainly contributes to the risk of emerging resistance to antimicrobials, an issue that is high on the agenda of the Department of Health and Social Care and the medical community globally.
2. Antibiotic choice and dose. Effective antibiotic therapy requires the presence of therapeutic drug levels at the site of the infected tissue. This depends on both bioavailability and tissue penetration. Optimising antibiotic choice will require a programme of work that may include techniques such as microdialysis of tissue fluid at the site of deep surgical infection.

Trial registration

This trial is registered as ISRCTN91566927.

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Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Some of the material in this chapter has previously been published in our description of the trial, reproduced from Li *et al.*[1] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Scientific background

Infections involving bones and joints are increasingly common. In the NHS in the UK, approximately 250,000 orthopaedic operations are performed annually, including 160,000 hip and knee replacements.[2] Around 1% of these are reported to have been complicated by postoperative infection.[3] In addition, there are around 5000 diabetic foot infections with associated osteomyelitis and a smaller number of infections of the axial skeleton. Treatment costs are estimated to be between £20,000 and £40,000 per patient.[4–6] Many consider a prolonged course (4–6 weeks) of intravenous (IV) antibiotics to be the 'gold standard' during the early phase of treatment for bone and joint infections.[7–9] However, such practice derives from an era prior to properly embedded pharmacokinetic principles, during which a widely held view was established that IV therapy is 'stronger' than PO therapy. As a result, IV antibiotic therapy is often preferred to oral (PO) therapy and has become an accepted standard of care even for many non-acute infections. The evidence base supporting this practice is, however, limited and there is a growing body of literature from randomised controlled trials (RCTs) and pharmacokinetic studies that suggest that an early switch to PO antibiotics is as effective as continued IV antibiotics. These studies have included patients with pneumonia,[10] urinary tract infections,[11] low-risk neutropenic sepsis,[12] skin and soft tissue infections[13] and endocarditis caused by *Staphylococcus aureus*.[14] There are no large RCTs of PO versus IV antibiotics for bone and joint infection but, provided that agents are carefully chosen with respect to bioavailability and tissue penetration, there is no biologically plausible reason to believe that bone and joint infections should be any different. A Cochrane review of five small trials involving a total 180 participants with bone or joint infection showed no benefit of IV as compared with PO therapy.[14,15] The largest single trial in this meta-analysis comprised 59 patients and the authors concluded that there is currently insufficient evidence to inform a widespread change in practice. Subsequent to this meta-analysis, a further trial involving 42 patients with *S. aureus* osteomyelitis, who were randomised to either IV cloxacillin or PO combination therapy with co-trimoxazole and rifampicin, showed similar results.[16] Observational studies have reported high success rates for prosthetic joint infection managed by two-stage revision and a shortened course of IV antibiotics or use of antibiotic cement spacers,[17,18] but observational comparisons are prone to confounding by indication whereby, for example, only those patients with a better underlying prognosis are switched early to PO antibiotics.

Prolonged IV antibiotic therapy mandates placement of an IV vascular access device, which carries a risk of complications such as catheter-related infection and thromboembolic disease.[6,19] PO antibiotic therapy mitigates such risks,[20,21] is more convenient for the patient and is less costly. On the other hand, PO therapy carries a greater risk of poor adherence, gastrointestinal intolerance and variable serum levels related to drug bioavailability.

Nonetheless, for the majority of bone and joint infections, clinicians are able to identify an appropriate PO antibiotic regimen with high PO bioavailability and good tissue penetration. This strategy, however, has not yet been compared with IV treatment in a large clinical trial. Therefore, we set out to address this issue.

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Initially, we conducted a single-centre pilot study that concluded in March 2013.[1] The results were reviewed by an independent Data Monitoring Committee (DMC), which advised that it was safe and appropriate to extend the trial. Thereafter, we broadened recruitment to multiple centres and transferred the data from the 228 participants in the pilot study to the database for a multicentre trial, the findings of which are reported here.

The Oral versus IntraVenous Antibiotics (OVIVA) trial was funded by the Health Technology Assessment (HTA) programme. The trial was in full compliance with the Helsinki Declaration[22] and has ethics approval (Research Ethics Committee reference number 09/H0604/109 for the single-centre pilot study and Research Ethics Committee reference number 13/SC/0016 for the multicentre trial) from the NHS health research authority.

Explanation of rationale

The objective of the study was to compare the efficacy and safety of IV versus PO antibiotic therapy for patients with bone and joint infection. Six weeks of IV therapy is the current standard of care for some or all of the patients in the hospital trusts that took part in this study. Antibiotics commonly used for IV therapy are often not suitable for oral use (because they are not absorbed) and PO antibiotics are often not suitable for IV use (either because an IV preparation is not available or because they require more frequent dosing than is logistically practical with outpatient IV therapy). It would not, therefore, have been possible simply to randomise the route of administration without this affecting the choice of antibiotic. The choice of antibiotic was subject to patient factors, the organisms identified and the site of infection, and the preferred antibiotic may have changed during treatment as laboratory results were returned or in response to drug reactions. Thus, it was not feasible to develop a protocol specifying particular antibiotics to cover each eventuality for either IV or PO antibiotic choice. In this study, therefore, we randomised participants to an PO or IV 'strategy'. The choice of individual antibiotics within the randomised strategy was made by a clinician specialised in managing clinical infection and was based on bioavailability, side effect profile, spectrum of activity and, while waiting for culture results, patient risk factors for resistant organisms.

Health economic rationale

The objective of the health economics analysis was to explore the cost-effectiveness of IV antibiotics compared with PO antibiotics. Cost-effectiveness is judged using incremental costs per health outcome. Two analyses were planned in the economic evaluation: a cost–utility analysis (CUA) using quality-adjusted life-years (QALYs) as the health outcome (cost per QALY gained) and a cost-effectiveness analysis (CEA) using definitive failures as an outcome (cost per definitive failure averted). As PO antibiotics were found to be non-inferior to IV antibiotics, the CEA was not carried out based on the assumption that there would be no difference by more than the predefined non-inferiority margin in the number of definitive treatment failures. A CEA would not be informative under these conditions. The health economic analyses focus on the CUA, analysing differences in health-related quality of life (QALYs) and differences in costs between treatment arms. The planned primary health economic analysis was within trial and had a time horizon of 12 months. The intention-to-treat (ITT) population was used. The planned secondary analysis was an extrapolation of trial results beyond the 12 months' follow-up. However, as there was no difference in failure rate between PO and IV antibiotics, extrapolation was not necessary, therefore, only the primary health economic analysis is presented.

Chapter 2 Methods

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Trial design

The trial was a parallel-group, unblinded, non-inferiority multicentre (1 : 1) RCT.

Trial participants

Participants were recruited from the following 26 secondary care centres, all of which are NHS hospitals in England and Scotland:

1. Birmingham Heartlands Hospitals
2. Bristol Royal Infirmary University Hospitals
3. Cambridge University Hospitals
4. Gartnavel General Hospital, Greater Glasgow and Clyde
5. Guy's and St Thomas' Hospitals, London
6. Hull and East Yorkshire NHS Trust
7. Leeds Teaching Hospitals
8. Newcastle upon Tyne Hospitals
9. NHS Lothian Hospitals, Edinburgh
10. Oxford University Hospitals
11. Royal Free Hospital, London
12. Royal National Orthopaedic Hospital, Stanmore
13. Royal Hallamshire Hospital, Sheffield
14. Royal Liverpool and Broadgreen University Hospitals
15. NHS Tayside, Dundee
16. Tunbridge Wells Hospital, Kent
17. Brighton and Sussex University Hospitals
18. Wansbeck Hospital, Northumbria
19. Medway Maritime Hospital, Kent
20. Norfolk and Norwich Hospitals
21. Queen Elizabeth Hospital, King's Lynn
22. Blackpool Teaching Hospitals
23. Northwick Park Hospital, London
24. Northampton General Hospital
25. University Hospitals of North Midlands, Stoke on Trent
26. Whittington Hospital, London.

All sites routinely used 6 weeks of IV antibiotic therapy as their standard initial treatment for some or all categories of bone and joint infection, and all were able to deliver IV antibiotics to patients after discharge from hospital.

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Participants were considered for inclusion when an infection specialist reviewed a patient with a bone or joint infection that was considered to require at least 6 weeks of antibiotic therapy. The contact was triggered through the routine care pathway, for example following referral by a surgical team, a referral from primary care direct to infectious disease services or by following up a laboratory result. Informed consent was obtained from each participant by research staff, trained in good clinical practice, after assessing their understanding of the patient information sheet (PIS). Eligibility was determined by the following inclusion and exclusion criteria.

Inclusion criteria

The participant had to meet each of the following criteria:

1. a clinical syndrome comprising any of the following – (1) localised pain, (2) localised erythema, (3) temperature > 38.0 °C or (4) a discharging sinus or wound
2. willing and able to give informed consent
3. aged ≥ 18 years
4. had received ≤ 7 days of IV therapy after an appropriate surgical intervention to treat bone or joint infection (regardless of presurgical antibiotics) or, if no surgical intervention was required, the patient had received ≤ 7 days of IV therapy after the start of planned curative treatment for the relevant clinical episode
5. life expectancy of > 1 year
6. bone and joint infection in one of the following categories –

    i. native osteomyelitis (i.e. bone infection without metalwork) including haematogenous or contiguous osteomyelitis
    ii. native joint sepsis treated by excision arthroplasty
    iii. prosthetic joint infection treated by debridement and retention, by one-stage revision or by excision of the prosthetic joint (with or without planned reimplantation)
    iv. orthopaedic device or bone-graft infection treated by debridement and retention, or by debridement and removal
    v. spinal infection, including discitis, osteomyelitis or epidural abscess.

Exclusion criteria

The participant was ineligible if he or she met any one of the following criteria:

1. *S. aureus* bacteraemia on presentation or within the previous month
2. bacterial endocarditis, either on presentation or within the previous month (note: there were no study mandated investigations, so participants were not required to have echocardiograms, blood cultures or any other investigations to exclude endocarditis in the absence of a clinical indication)
3. any other concomitant infection that, in the opinion of the clinician responsible for the patient, required a prolonged course of IV antibiotic therapy (e.g. mediastinal infection or central nervous system infection)
4. mild osteomyelitis, defined as bone infection that, in the opinion of the physician, would not usually require a 6-week course of IV antibiotic therapy
5. an infection for which there were no suitable antibiotic choices to permit randomisation between the two arms of the trial (e.g. when organisms were only sensitive to IV antibiotics)
6. prior enrolment in the trial
7. septic shock or systemic features requiring IV antibiotic therapy in the opinion of the treating clinician (the patient could be re-evaluated if these features resolved)
8. unlikely to comply with trial requirements following randomisation in the opinion of the investigator
9. clinical, histological or microbiological evidence of mycobacterial, fungal, parasitic or viral aetiology of the infection
10. receiving an investigational medical product as part of another clinical trial.

The use of antibiotic-loaded cement in spacers, bone substitutes or beads at the site of infection was not an exclusion criterion, but was recorded. Pregnancy, renal failure and liver failure were not exclusion criteria, provided that suitable antibiotic options could be identified for both IV and PO therapy prior to randomisation.

Randomisation

An electronic randomisation service, with telephone back-up if necessary, was provided through a clinical trials unit (CTU). After confirming the patient's eligibility, the randomisation service assigned a sequentially allocated study number and informed the investigator of the treatment allocation in real time and by confirmatory e-mail. Randomisation was stratified by site to take account of variation in clinical practice between centres.

The local clinician or study nurse was responsible for documenting participants' enrolment in their clinical notes and for informing the participant's general practitioner (GP).

Interventions

Eligible patients were randomised (1 : 1) to complete the first 6 weeks of antibiotic therapy with either IV or PO antibiotic therapy. The selection of individual antibiotics within the allocated strategy (i.e. PO or IV antibiotics) was the responsibility of the infection specialist caring for the patient, based on microbiological assessments, the side effect profile, patient preferences and epidemiological factors suggesting the likelihood of antibiotic resistance. In the event of a culture-negative bone or joint infection (or when there was a delay in availability of culture results), the infection specialist selected the most appropriate empiric therapy. When new information became available, the infection specialist was permitted to alter the choice of antibiotic agent according to clinical need. If the participant remained within the allocated administration strategy, they remained within protocol; if this was not possible, the participant was deemed to have met a secondary end point (i.e. early termination of the randomised strategy).

Patients randomised to the IV strategy were expected to complete 6 weeks of IV antibiotics. When necessary for optimal care, clinicians were permitted to use adjunctive PO agents in patients treated with IV therapy (e.g. PO rifampicin as adjunctive therapy for biofilm-related staphylococcal infection). Patients randomised to PO therapy were expected to commence their randomised strategy as soon as possible but were permitted to remain on IV therapy for up to 7 days from the start of the treatment episode, which was most commonly the date of surgical intervention, without being considered an end point. This provided an opportunity for complete recovery from anaesthesia and for antibiotic selection based on culture and susceptibility testing after surgery. If a participant who was randomised to PO therapy required IV antibiotic therapy for an unrelated intercurrent illness during the initial 6 weeks of treatment, or experienced vomiting, inability to swallow or other concern about absorption of PO medication, then IV antibiotic therapy could be substituted for up to 5 days. If IV antibiotic prescribing exceeded the limits set in the PO strategy, the patient was deemed to have met a secondary end point but still contributed to the 'ITT' analysis, and study follow-up therefore continued.

If at any point the randomised strategy (IV or PO) was no longer compatible with good clinical care, then the study participant was withdrawn from their randomised treatment arm and an end point was recorded. Appropriate reasons for discontinuing the allocated treatment were, for example, no suitable medication was available within the allocated strategy because of adverse reactions, contraindications and susceptibility testing results. Failure to maintain IV access was considered a legitimate reason for discontinuing IV antibiotics and switching to PO antibiotics to complete the first 6 weeks. In such cases, the event was recorded as a secondary end point, which was most commonly an early exit from allocated treatment strategy. However, a wound discharge, superficial erythema or other clinical sign related to infection or resolution of infection was not an appropriate indication for changing PO to IV, or vice versa, as there was equipoise regarding efficacy.

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For any patient who was withdrawn from their randomised strategy, each case was discussed with the study chief investigator or delegate of the chief investigator beforehand. Changing the antibiotic while remaining within the allocated strategy did not need discussion, but such decisions were made by a clinician with appropriate training in managing infection. Patients who were withdrawn from the allocated strategy for any reason continued to be followed up according to the trial protocol (unless they specifically declined this) and were included in 'ITT' analysis of efficacy, but not in the 'according-to-protocol' analysis (unless they had completed at least 4 weeks within their randomised strategy).

Dose adjustments based on renal or hepatic function, drug interactions or other factors were permitted in accordance with drug labelling information: the *British National Formulary* (BNF) and local pharmacy guidelines.

Follow-on antibiotic treatment after the initial 6 weeks was allowed in either arm of the trial, but the choice of agent, duration and route of administration were not governed by the trial protocol.

All systemic antibiotics used (including dose, route of administration and duration) were recorded in the case report form (CRF) from the date of randomisation to final follow-up at 1 year. Local antibiotic use in cement or bone fillers was recorded but topical antibiotic use for superficial wounds was not.

There were no formal withdrawal criteria in this study other than at the request of a participant. All patients were free to withdraw their consent at any time; if they elected to withdraw from the allocated treatment strategy during the randomised treatment phase, they were deemed to have met a secondary end point but were still followed up and included in the analysis, provided that appropriate consent had been obtained.

Assessments

Data on inclusion criteria, patient characteristics, operative details and comorbidities were collected at the baseline/enrolment visit and entered onto the web-based database by the trial sites.

While an inpatient, study clinician or research nurse maintained contact with the clinical team to identify potential end points, and to ensure implementation of the randomised antibiotic strategy. Following hospital discharge, participants were seen according to clinically determined follow-up plans. Trial-specific clinical data were obtained from either face-to-face contact with the participants or from the relevant case records at 6 weeks (range day 21 to day 63), 4 months (range day 70 to day 180) and 1 year (range day 250 to day 420). Research staff at the recruiting centre were responsible for entering the data from clinical reviews. If the patient did not attend clinic within the specified date ranges, the investigator arranged a telephone review with the participant or the participant's GP to identify potential end points or serious adverse events (SAEs). If, based on the telephone discussion, a further clinical review was indicated, the investigator facilitated this and advised the patient accordingly.

A study clinician reviewed the source documents from routine care visits when completing investigator reviews. They recorded:

- microbiology and histology results and date of discharge (first review only)
- outpatient visits since randomisation
- SAEs
- readmissions for inpatient care
- type of IV catheter (line) used and any line-related complications
- episodes of *Clostridium difficile*-associated diarrhoea
- antibiotic use, including dosage, route and model of care (e.g., district nurse, self-administered or daily clinic visits)
- presence or absence of any potential end points
- reasons for not completing the planned antibiotic course (if applicable).

The EuroQol-5 Dimensions, three-level version (EQ-5D-3L) questionnaires to assess quality of life were requested at baseline, day 14, day 42, day 120 and day 365. The baseline EuroQol-5 Dimensions (EQ-5D) data were entered by the researcher and then filed in the site file. Subsequent EQ-5D questionnaires were handed to participants with prepaid envelopes to the central CTU in Oxford for data entry and filing. EQ-5D data were not routinely collected during the single-centre pilot study.

Oxford Hip Score (OHS) or Oxford Knee Score (OKS) questionnaires were given to patients with an infection in the hip or knee. Returns were requested at baseline, day 120 and day 365. Baseline data were entered at trial sites, but subsequent returns were sent directly to Oxford for data entry and filing.

A subset of participants was monitored through a Medication Event Monitoring System (MEMS). These consist of tablet containers with a cap that records every opening with a date and time stamp, which subsequently can be downloaded for analysis permitting monitoring of medication adherence.

Objectives

The primary objective was to determine whether or not PO antibiotics are non-inferior to IV antibiotics for serious bone and joint infection, as judged by the proportion of patients experiencing definitive treatment failure during 1-year of follow-up.

Secondary objectives were to compare the following end points according to treatment allocation:

1. SAEs, including death (i.e. all cause) according to treatment allocation
2. line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line)
3. *C. difficile*-associated diarrhoea
4. 'probable' and 'possible' treatment failure as composites with definitive treatment failure
5. early termination of the planned 6-week period of PO or IV antibiotics because of adverse events, patient preference or any other reason
6. resource allocation using (1) length of inpatient hospital stay, (2) frequency of outpatient visits and (3) antibiotic prescribing costs
7. quality of life, as evaluated by EQ-5D questionnaire
8. OHS and OKS (when infection was in the hip or knee)
9. adherence, as indicated by MEMS in a subset of participants. [In a subset of sites (i.e. Oxford University Hospitals, Guy's and St Thomas' Hospitals Trust, Royal Free Hospital Trust and Royal National Orthopaedic Hospital), PO antibiotics were dispensed to patients in pill containers with MEMS.]

Outcomes

Potential primary end points were identified through post-randomisation prospective surveillance, and reviewed by an end-point committee blind to the treatment group. The primary end point was failure of infection treatment, for which definite failure was indicated by one or more of the following:

1. isolating bacteria from two or more samples of bone/spine/periprosthetic tissue, when the bacteria were phenotypically indistinguishable
2. a pathogenic organism (e.g. *S. aureus* but not *S. epidermidis*) on a single, closed aspirate or biopsy of native bone or spine
3. diagnostic histology on bone/periprosthetic tissue
4. formation of a draining sinus tract arising from bone/prosthesis
5. recurrence of frank pus adjacent to the bone/prosthesis.

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Secondary end points were:

1. SAEs, including death (i.e. all cause) according to treatment allocation
2. line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line)
3. 'probable' or 'possible' treatment failure as composites with definitive treatment failure – these were determined by a blinded end-point committee review and determined according to the following criteria:
   (a) loosening of a prosthesis, confirmed radiologically, or
   (b) non-union of a fracture after 6 months, confirmed radiologically, or
   (c) superficial spreading erythema, treated as cellulitis with an antibiotic for > 1 week, when results from deep tissue samples did not meet the primary end point as described above

   when appropriate, deep tissue samples were sent for microbiology and the results of culture were negative, and either (a), (b) or (c) were met, the end point was regarded as 'possible'. On the other hand, when deep tissue samples were not sent for microbiology, and either (a), (b) or (c) were met, then the end point was regarded as 'probable'

4. early termination of the planned 6-week period of PO or IV antibiotics because of adverse events, patient preference or any other reason
5. resource allocation determined by (1) length of inpatient hospital stay, (2) frequency of outpatient visits and (3) antibiotic prescribing costs
6. quality of life evaluated by EQ-5D questionnaire
7. OHS and OKS (when infection was in the hip or knee)
8. adherence to PO medication.

The study clinicians determined secondary end points 1, 2, 4 and 5. The blinded end-point review committee determined primary end points and secondary end point 3, by reviewing relevant clinical notes redacted for personal details and any information that might have betrayed the treatment allocation. Participant questionnaires determined secondary end points 6 and 7. Secondary end point 8 was determined by MEMS at four sentinel sites.

Adherence and Medication Event Monitoring Systems

Patient adherence to antibiotic therapy may directly influence the outcome of treatment. In order to avoid intrusion and to minimise undue influence on patient behaviour, participants did not receive any direct antibiotic adherence support (such as text message reminders or telephone monitoring), but the importance of adherence was explained at the time of recruitment and reinforced at the time of discharge. The PIS included information written by the patient representatives explaining the importance and underlying rationale of medication adherence.

In order to validate adherence, selected sites (i.e. Oxford University Hospitals, Guy's and St Thomas' Hospitals, The Royal National Orthopaedic Hospital and The Royal Free Hospital, London), dispensed PO antibiotics in pill containers with MEMS.[23,24] Sensors in the pill container lids (caps) detected opening and closing and recorded these events with a time and date stamp. The sensor data were downloaded and read at a later date to assess whether or not patients had opened their bottles at times consistent with their prescription. MEMS were used only with specific consent from participants. If more than one antibiotic was prescribed, MEMS sensors were used for the more frequently dosed antibiotic.

Safety

As the OVIVA trial did not involve randomisation to a specific therapy, it was not a 'Clinical Trial of an Investigational Medicinal Product', as defined by the European Union directive 2001/20/EC.[25] Safety reporting therefore referred to the trial sponsor and the DMC. All SAEs identified within a year of randomisation were recorded.

If an investigator became aware of an unexpected SAE during the trial, he or she contacted the chief investigator who clarified clinical details and reported the SAE to the sponsor. If, in the opinion of the chief investigator or the sponsor, an unexpected SAE might have been relevant to participant safety, a detailed report including an assessment of causality and severity was forwarded to the DMC. In turn, the DMC made a recommendation to the Trial Steering Committee regarding the safety of the trial in the light of this report.

Expected SAEs that did not undergo expedited reporting were defined as:

- complications of bone/joint surgery
- complications of the bone/joint infection for which the patient was undergoing treatment (including potential end points)
- drug reactions as detailed in the product literature [i.e. the summary of product characteristics (SmPC) or BNF]
- drug reactions for concurrent medications given for routine clinical care as detailed in the product literature (i.e. SmPC or BNF)
- intercurrent illness causally related to the comorbid conditions that the investigator believed were likely diagnoses, given the patient's history, age and other factors.

The investigators used their judgement, such that SAEs that technically met the definitions above for expectedness, but that seemed unexpected in terms of severity, duration or other factors, may have been reported as unexpected.

Statistical methods

Full details of the statistical methods used are detailed in a statistical analysis plan (see *Appendix 1*), which was agreed and signed off prior to locking the database.

Sample size

An initial sample size estimation of 1050 was based on an expected overall failure rate of 5% and a non-inferiority margin of 5% (or a relative increase of 100%), with a one-sided alpha = 0.05, 90% power and 10% loss to follow-up. This was derived from short-term follow-up in the single-centre pilot study in which 10 participants experienced a primary end point in the first 197 randomisations.

Pooled data from a planned interim analysis during the multicentre study demonstrated that the true event rate was likely to be closer to 12.5%. To account for this, we adjusted the non-inferiority margin to 7.5% (or a relative increase of 60%). As the final control group failure rate remained unknown, recruitment continued as planned until October 2015 to achieve the largest possible sample size within the original target, and to optimise the potential utility of subgroup analyses. The DMC and ethics committee approved this as an amendment to the protocol.

Primary analysis

The proportions of participants experiencing a primary end point at 1-year follow-up (definitive treatment failure as adjudicated by a blinded end-point review committee) were tabulated by randomised strategy (i.e. PO vs. IV therapy). Non-inferiority was defined as the absolute, upper 90% confidence interval (CI)

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around the unadjusted difference (PO vs. IV) being < 7.5%. The primary analysis was based on the ITT population, whereby all participants were included based on their randomised strategy (PO vs. IV strategy). Missing end-point data were handled by multiple imputation. Supporting analysis included a complete-case analysis, a per-protocol (PP) analysis and an analysis whereby those with missing end points were assumed not to have experienced a definitive treatment failure. Sensitivity analyses explored the impact of informatively missing data.

Secondary analyses

Secondary analyses focused on consistency of point estimates and 95% CI, rather than formal comparisons with the 7.5% non-inferiority margin. Adjusted quantile regression models or rank sum tests were used to compare continuous secondary outcomes, and proportions of participants with secondary end points were presented (including chi-squared tests). Interaction tests were used to determine the consistency of treatment effects by prespecified subgroups, including the type of baseline surgical procedure, infecting pathogen and the clinician's specified antibiotic intentions, as recorded prior to randomisation, and whether or not this planned antibiotic regimen included rifampicin.

Deviations from the statistical analysis plan

Additional post hoc subgroup analyses performed were:

- metal retained versus no metal retained in baseline surgical procedure
- known pathogen versus pathogen unknown
- participants with and without peripheral vascular disease.

Software employed

Analyses were undertaken using Stata® (version 14SE, StataCorp LP, College Station, TX, USA).

Randomisation

A randomisation list, stratified by site and prepared by a statistician, was held securely by a CTU. The randomisation sequence was created using Stata 12IC statistical software and was stratified by centre with a 1 : 1 allocation using random blocks of size 8–14. Allocation concealment was achieved through the use of sequentially allocated study numbers. After confirming a patient's eligibility, the study clinician contacted the CTU via a website link (with telephone back-up if required) to be provided with a study number and the associated randomised treatment allocation (PO vs. IV for the first 6 weeks of antibiotics). An automated e-mail confirming these data was then forwarded to the clinician randomising the patient. All participants were randomised after confirmation of eligibility but within 7 days of the start of their treatment episode.

Blinding

The study was open label. Blinding was not possible, as we considered that giving prolonged IV placebo would pose an unnecessary risk to participants and, therefore, would be unethical. Because an open-label study is at risk of bias, we appointed an end-point review committee. The end-point review committee was composed of three independent clinicians (two infectious diseases specialists and one orthopaedic surgeon) with expertise in the management of orthopaedic infections.

All relevant notes relating to a potential end point were reviewed and redacted for both personal identifiable information and specifics of antibiotic treatment or IV line insertion, which could have indicated the route of administration of antibiotics. The end-point review committee was therefore blind to treatment allocation. The redacted notes were forwarded to the end-point review committee, which examined them against objective criteria, to determine whether or not an end point had been met, either by consensus or by a vote called by the chairperson if consensus could not be reached.

The end-point review committee was only required to review definite or potential treatment failures. All other end points were determined directly by the local study clinicians.

Summary of changes to the project protocol

- Adjustment of non-inferiority margin as described under *Sample size*.
- Extension of recruitment period at no additional cost.

Health economic analysis methods

The economic evaluation is based on health-care resource use and quality-of-life data collected during the trial. All costs and health outcomes were measured and collected within 1 year, so that no discount rate was applied.

Resource use

Costs were measured from a NHS and Personal Social Services perspective. Resource use included antibiotic medication, IV administration and complications, and inpatient stays. These were completed for the time periods of 42, 120 and 365 days following randomisation. Costs for medication were obtained from the BNF.[26] Inpatient stays were valued using NHS reference costs[27] and IV administration resources and costs were taken from the literature[28,29] and adjusted for inflation using the Hospital and Community Health Index.[30] Costs were reported for 2015 in Great British pounds. Antibiotic resource use includes all antibiotics prescribed to each participant in the 12-month follow-up period. Inpatient stays are per bed-day, and IV administration includes the cost of IV line insertion and removal for each IV episode per participant, cost of line complications when a new line is needed and the cost of the outpatient parenteral antimicrobial therapy (OPAT) team, if applicable.

Total costs per participant were calculated by assigning unit costs to within-trial resource use for each participant.[29] Unit costs and their sources are presented in *Table 1*.

Health outcomes

Outcomes are measured using QALYs. QALYs are a combination of both quality and length of life. Quality-of-life data were collected using the EQ-5D-3L,[31] administered at baseline, at 14 days, 42 days, 120 days and 365 days and if an end point or SAE occurred. The EQ-5D data collected when a SAE occurred were subsequently not used, as the available data were insufficient to provide additional information for the analysis. The EQ-5D-3L is a generic quality-of-life measure comprising five questions and a visual analogue scale (VAS). The questions cover five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There are three levels of severity for each domain ('no pain', 'moderate pain' and 'extreme pain'). The EQ-5D instrument provides 243 predefined health states. Responses are pooled into a three-digit number labelling the respondent's health state (from '111', meaning no health-related problems, to '333', meaning extreme health-related problems in all five domains).[32]

The EQ-5D-3L responses were converted to utility measures using the tariff developed for the UK general population.[33] This utility is combined with the length of time the person is in each health state using standard area-under-the-curve methods to calculate QALYs. Patient-specific QALYs were estimated using

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TABLE 1 Unit costs and sources

Resource	Unit cost	Source
Antibiotic	Various	BNF[26]
Inpatient stay	£295.80 per overnight stay	*NHS Reference Costs 2014 to 2015*[27]
IV administration		
Insertion: PICC[a]	£190	Expert opinion
Removal	£34.12	Expert opinion
OPAT type		
District nurse	£58 per hour	*NHS Reference Costs 2014 to 2015*[27]
Infusion centre attendance	£109 per hour	*NHS Reference Costs 2014 to 2015*[27]

PICC, peripherally inserted central catheter.
a Only six patients were reported to have a Hickman line inserted and the majority of patients had a PICC. To be consistent within the IV arm of the trial, we assumed a constant cost for a PICC for all patients. A Hickman line is likely to increase costs only marginally in the IV arm as these lines involve a surgeon's time to be inserted.
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utility values from each follow-up point and weighting each time interval by the patient's utility during that period. A utility score of 1 is equivalent to full health and 0 is equivalent to death. It is possible to have a negative utility score, for which the patient's health state is worse than death. Discrete changes in utility values between follow-up time points were assumed to be linear.

Analysis

The total cost per participant in each intervention was summed and divided by the number of participants in each arm to calculate the mean cost per participant in each arm, along with the difference in means and 95% CI.

The mean QALY per participant for each intervention was calculated by summing all participants' QALYs and dividing by the number of participants in that intervention arm. The difference in the means was calculated along with 95% CIs.

The analysis was carried out in Stata version 14.0. Complete cases were analysed initially and multiple imputation was used to explore the effect of missing data on the analysis.

Missing data

The nature of the missing data was analysed and an appropriate method to replace missing data utilised.[34,35] Missing data for resource use and EQ-5D-3L were handled using multiple imputation, which requires less strong assumptions than complete-case analysis. Multiple imputation requires a more relaxed assumption that data are missing at random. The probability of having missing data is independent of unobserved values and the missing data may depend on observed data.[36] Missing resource and quality-of-life data were imputed using multiple imputation by chained equation.[37]

The regression analyses used to impute missing data included information on 'baseline surgical procedures'.

The following assumptions were made:

- the cost of a line insertion and removal was applied to the initial 6-week period of the intervention.[29] In addition, it was assumed that an IV episode with a gap of ≤ 2 days between IV drugs did not require a new line to be inserted and a cost was not applied for insertion/removal; if the gap between episodes was > 2 days, it was assumed that a new line had to be inserted and the old line was removed, and a cost was assigned accordingly
- the OPAT type recorded at the 42-day follow-up visit was used for each participant for all IV episodes in the 12-month follow-up period[29]
- any durations of antibiotics, IV episodes and inpatient stays per participant were truncated at 365 days, as the follow-up period is 365 days
- OPAT costs were applied at 1 hour per day, if applicable
- participants with an OPAT type of 'infusion centre' had a weighted cost of two out of five to self-administrating and three out of five to district nurse applied to the length of IV episode following discharge from hospital; this was the proportion of district nurse to self-administering OPAT witnessed in the trial
- for participants with missing data for OPAT type, a weighted average cost of two out of five to self-administrating and three out of five to district nurse was applied to the length of IV episode
- for participants with missing data for IV line type, the cost of a peripherally inserted central catheter line was used as this was used by the majority of participants during the trial.

Sensitivity analysis

Instead of using the above weighted average for participants with missing OPAT type, two scenarios were explored: applying solely the cost of a district nurse, and applying solely the cost of self-administration.

To explore the uncertainty around the cost and QALY differences and the resulting incremental cost-effectiveness ratio (ICER), a non-parametric bootstrapping technique was employed with 1000 iterations. Results are presented using a cost-effectiveness plane, showing all 1000 cost-effectiveness pairs.

Long-term outcomes

Owing to the non-inferiority margin being met in the trial, the extrapolation of failure rates was not carried out as there would have been no difference in rates extrapolated forward.

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Chapter 3 Results

Recruitment

The timeline of recruitment into the study was as follows:

- date of start of recruitment – 26 March 2013, start of main study; 3 June 2010, start of internal pilot
- date of end of recruitment – 31 October 2015
- date of end follow-up – 31 October 2016
- date of final analysis – 1 November 2016–20 January 2017
- target number of subjects – 1054 (527 per arm) including the pilot.

Originally, recruitment to the OVIVA study was to conclude at the end of October 2014. Owing to the initial recruitment being lower than expected, the trial was granted an extension without additional funding. The above presented timelines take into account this extension.

Study participants

Information on screening, eligibility, randomisations and follow-up is shown in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram in *Figure 1*.

Screening logs were only available in the multicentre study and not all sites completed screening logs adequately. Therefore, the CONSORT flow diagram may overestimate conversion rates from screened to eligible and eligible to randomised participants.

Participants were excluded from the PP population if they received < 4 weeks of their allocated strategy for reasons other than possible or probable recurrence of infection and/or had missing data for the primary end point.

Data quality

Data collection and compliance

Data on inclusion criteria, patient characteristics, operative details and comorbidities were collected at the baseline/enrolment visit and entered onto the web-based database by the trial sites.

Three clinical reviews were performed for each participant during the follow-up:

- day 42 (accepted range day 21–63)
- day 120 (accepted range day 70–180)
- day 365 (accepted range day 250–420).

Clinical assessment compliance

Table 2 shows the data completeness for clinical assessments at three follow-up points. The number of missing baseline and follow-up CRFs may not coincide with the number of participants withdrawn or lost to follow-up at the relevant assessment time point. This is because CRFs could be completed to indicate participant withdrawal and loss to follow-up, as well as to record relevant clinical data up to the time of withdrawal/loss to follow-up.

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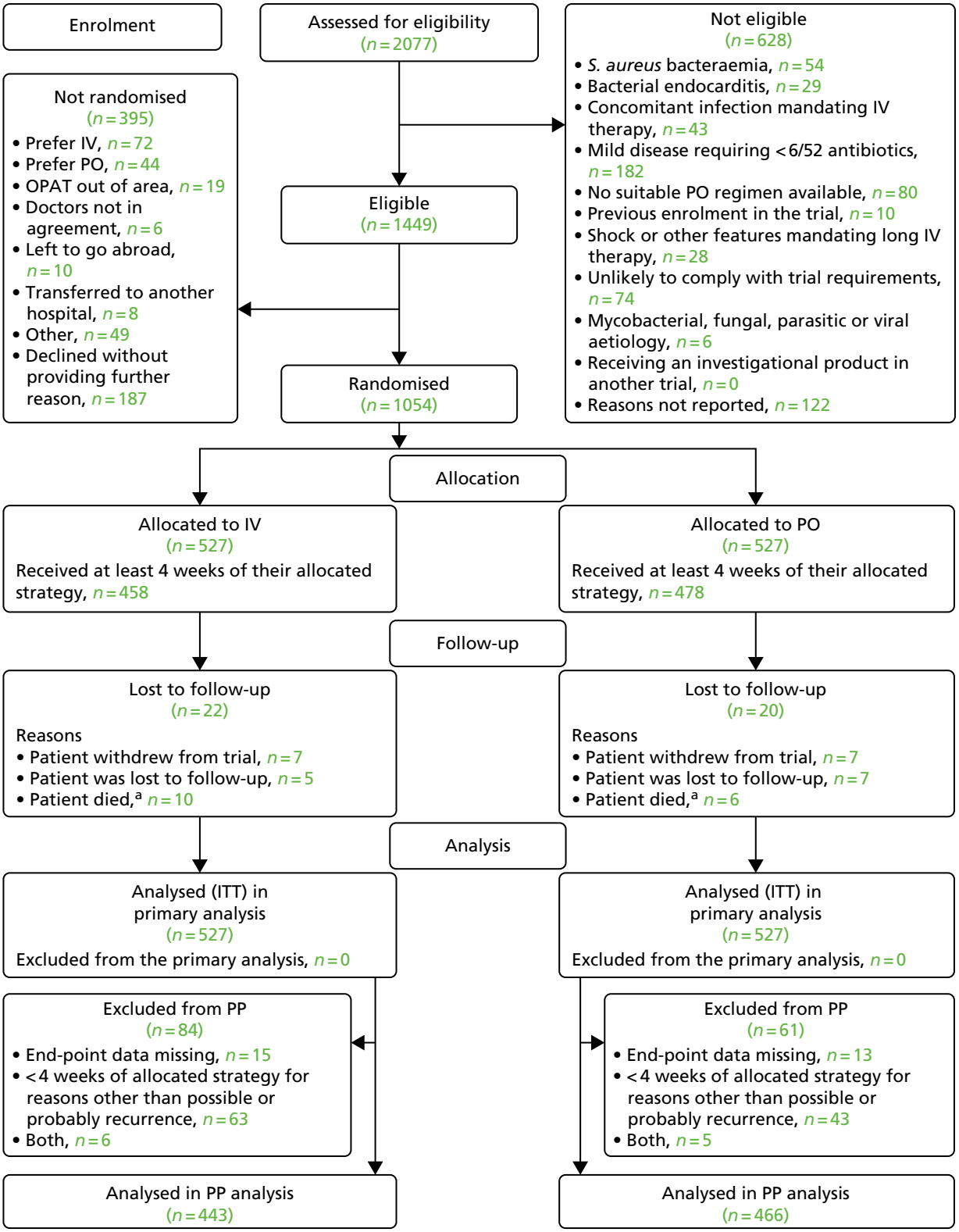


FIGURE 1 The OVIVA trial CONSORT flow diagram. a, An additional seven deaths were reported within the acceptable range for the day 365 follow-up. The final follow-up for these participants is not considered missing. These deaths are reported in *Serious adverse events*.

TABLE 2 Data compliance for clinical assessments

	Antibiotics								
	IV			PO			Total		
Assessment	Complete	Expected	%	Complete	Expected	%	Complete	Expected	%
Baseline	527	527	100.00	527	527	100.00	1054	1054	100.00
Day 42	523	527	99.24	523	527	99.24	1046	1054	99.24
Day 120	517	527	98.10	521	527	98.86	1038	1054	98.48
Day 365	514	527	97.53	517	527	98.10	1031	1054	97.82

Questionnaire compliance

Some potential participants were willing to take part in the trial, but were unwilling to complete quality-of-life data. This contributed to the low compliance rate for the questionnaires (*Table 3*).

Although not routinely collected from 228 participants in pilot phase of the OVIVA study, 122 questionnaires were received for these participants (1 at day 14, 74 at day 42, 32 at day 120 and 15 at day 365). These data were included in the analysis of the EQ-5D-3L.

Table 4 displays the number of participants for whom the OHS and OKS could be calculated at the relevant time points. The OHS and OKS could be calculated when up to two items are missing. A low number of additional questionnaires were received for which the calculation of the OHS was not possible owing to missing items (4 at baseline, 2 at day 120 and 2 at day 365). A low number of additional questionnaires were received for which the calculation of the OKS was not possible owing to missing items (3 at day 120 and 2 at day 365). These questionnaires were not classed as complete and are not included any of the subsequent summaries and analyses.

Baseline characteristics

Trial site was the only stratification factor for randomisation in this trial. *Tables 5* and *6* provide an overview of the baseline data. As these data were collected on different CRFs, not all data were available for all randomised participants.

TABLE 3 The EQ-5D compliance for OVIVA2[a] participants

	Antibiotics								
	IV			PO			Total		
Assessment	Complete	Expected	%	Complete	Expected	%	Complete	Expected	%
Baseline	386	414	93.24	388	412	94.17	774	826	93.70
Day 14	307	414	74.15	308	412	74.76	615	826	74.46
Day 42	326	414	78.74	336	412	81.55	662	826	80.15
Day 120	295	414	71.26	286	412	69.42	581	826	70.34
Day 365	285	414	68.84	276	412	66.99	561	826	67.92

a This table summarises EQ-5D-3L data availability for pariticipants recruited after the pilot study.

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TABLE 4 Oxford Hip and Oxford Knee Scores

	Antibiotics								
	IV			PO			Total		
Assessment	Complete	Expected	%	Complete	Expected	%	Complete	Expected	%
OHS									
Baseline	74	87	85.06	71	81	87.65	145	168	86.31
Day 120	64	87	73.56	59	81	72.84	123	168	73.21
Day 365	60	87	68.97	57	81	70.37	117	168	69.64
OKS									
Baseline	99	111	89.19	88	98	89.80	187	209	89.47
Day 120	75	111	67.57	69	98	70.41	144	209	68.90
Day 365	75	111	67.57	67	98	68.37	142	209	67.94

Table 7 shows information on histology and microbiology results and the diagnostic certainty of infection as determined by baseline criteria. Although these samples were taken at trial entry, data were collected at the day 42 CRF. Therefore, data for eight participants were missing, as this form was received for only 1046 participants. One further participant, who was withdrawn soon after randomisation, also has missing data for their histology and microbiology. This accounts for nine missing data points in this table. For those participants who did not fulfil the predefined definition for definite infection, an independent blinded committee reviewed the case records to assign categorisation.

Note that there were participants who did not fulfil the definition of infection at baseline in accordance with the protocol but who were treated for infection on clinical grounds. These participants are summarised under 'infection status unclear'. A decision was made by the trial team to include these participants into the 'possible infection' category in all subsequent summaries.

Numbers analysed

The following patient populations were utilised in the analysis:

Intention to treat

All randomised participants were analysed according to their allocated intervention.

Modified intention-to-treat analysis

All randomised participants with both baseline and at least one post-baseline assessment for patient reported outcomes. For all other outcomes, randomised participants with at least one post-baseline assessment. Participants were excluded from this analysis if relevant baseline covariates (when relevant) were not available. In other words, the modified intention-to-treat analysis (MITT) population was the complete-cases subset of the ITT population.

Per protocol

The PP population was defined as all participants who received at least 4 weeks of their randomised strategy and, if in the PO group, did not exceed the limits set for the use of IV antibiotics (i.e. 5 continuous days at any one time). Participants who were recorded to have exited early from their randomised strategy owing to possible or probable recurrence of infection were also included in the PP population. Participants were included in the PP analyses if sufficient outcome and baseline data (when relevant) were available.

TABLE 5 Baseline characteristics

Trial site and characteristics[a]	Antibiotic, *n* (%)		Total (*N* = 1054), *n* (%)
	IV (*N* = 527)	PO (*N* = 527)	
Oxford University Hospitals	256 (48.58)	256 (48.58)	512 (48.58)
Bristol Royal Infirmary	3 (0.57)	3 (0.57)	6 (0.57)
Western General Hospital Edinburgh	5 (0.95)	3 (0.57)	8 (0.76)
Guy's and St Thomas London	19 (3.61)	17 (3.23)	36 (3.42)
Royal Free London	23 (4.36)	22 (4.17)	45 (4.27)
Queen Elizabeth Hospital King's Lynn	0 (0.00)	1 (0.19)	1 (0.09)
Royal Liverpool University Hospital	36 (6.83)	34 (6.45)	70 (6.64)
Addenbrookes Hospital Cambridge	25 (4.74)	24 (4.55)	49 (4.65)
Royal Hallamshire Hospital Sheffield	2 (0.38)	0 (0.00)	2 (0.19)
Royal Victoria Infirmary Newcastle	1 (0.19)	1 (0.19)	2 (0.19)
Ninewells Hospital Dundee	7 (1.33)	7 (1.33)	14 (1.33)
Gartnaval Hospital Glasgow	23 (4.36)	21 (3.98)	44 (4.17)
Birmingham Heartlands	23 (4.36)	25 (4.74)	48 (4.55)
Royal National Orthopaedic Hospital Stanmore	63 (11.95)	63 (11.95)	126 (11.95)
Hull Royal Infirmary	5 (0.95)	6 (1.14)	11 (1.04)
Medway Hospital	0 (0.00)	2 (0.38)	2 (0.19)
University Hospital of North Staffordshire	0 (0.00)	1 (0.19)	1 (0.09)
Leeds General Infirmary	14 (2.66)	14 (2.66)	28 (2.66)
Northampton General Hospital	4 (0.76)	1 (0.19)	5 (0.47)
Maidstone and Tunbridge Wells	1 (0.19)	3 (0.57)	4 (0.38)
Royal Sussex County Hospital Brighton	2 (0.38)	5 (0.95)	7 (0.66)
Northumbria NHS Trust	5 (0.95)	8 (1.52)	13 (1.23)
Norfolk and Norwich University Hospital	4 (0.76)	2 (0.38)	6 (0.57)
Blackpool Teaching Hospitals	2 (0.38)	4 (0.76)	6 (0.57)
Northwick Park London	3 (0.57)	3 (0.57)	6 (0.57)
Whittington Hospital London	1 (0.19)	1 (0.19)	2 (0.19)
Gender[a]			
Male	320 (60.72)	358 (67.93)	678 (64.33)
Female	207 (39.28)	169 (32.07)	376 (35.67)
Age (years)[b]	61 (49–70) (18–92)	60 (49–70) (18–91)	60 (49–70) (18–92)

a Frequency and percentages are displayed.
b Median, interquartile range and range are displayed.

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TABLE 6 Baseline summaries: data collected at enrolment visit

Clinical variable	Antibiotic		Total
	IV (*N* = 527[a]), *n* (%)	PO (*N* = 527[a]), *n* (%)	(*N* = 1054[a]), *n* (%)
Information on inclusion criteria[b]			
Localised pain	397 (75)	403 (76)	800 (76)
Localised erythema	226 (43)	207 (39)	433 (41)
Temperature > 38.0 °C	62 (12)	62 (12)	124 (12)
Discharging sinus/wound	296 (56)	285 (54)	581 (55)
Information on the baseline surgical procedure			
Chronic osteomyelitis debrided, no current implant or device	153 (29)	169 (32)	322 (31)
Chronic osteomyelitis as above, but not debrided	25 (4.7)	29 (5.5)	54 (5.1)
Implant or device present and retained	124 (24)	123 (23)	247 (23)
Removal of orthopaedic device for infection	89 (17)	78 (15)	167 (16)
Prosthetic joint implant removed	68 (13)	67 (13)	135 (13)
Prosthetic joint implant, one-stage revision	47 (8.9)	43 (8.2)	90 (8.5)
Discitis/spinal osteomyelitis/epidural abscess debrided	8 (1.5)	5 (1.0)	13 (1.2)
Discitis/spinal osteomyelitis/epidural abscess but not debrided	13 (2.5)	13 (2.5)	26 (2.5)
Information on anatomical site affected by the infection			
Left	225 (43)	240 (46)	465 (44)
Right	252 (48)	241 (46)	493 (47)
Bilateral[c]	50 (9.5)	46 (8.7)	96 (9.1)
Further information on anatomical site[d]			
Spinal infection	37 (7.0)	35 (6.6)	72 (6.8)
Upper limb infection	43 (8.2)	59 (11)	102 (9.7)
Lower limb infection	436 (83)	419 (80)	855 (81)
Other area of infection	12 (2.3)	14 (2.7)	26 (2.5)
Details on lower limb infections[e]	**n = *436***	**n = *418***	**n = *854***
Hip	110 (25)	104 (25)	214 (25)
Knee	133 (31)	115 (27)	248 (29)
Foot	89 (20)	86 (21)	175 (20)
Other area of lower limb infection	105 (24)	113 (27)	218 (26)
Operative findings			
Draining sinus arising from bone/prosthesis	177 (34)	142 (27)	319 (30)
Frank pus adjacent to bone/prosthesis	179 (34)	186 (35)	365 (35)
Information on local antibiotics used during the operation			
No	360 (68)	348 (66)	708 (67)
Cement	129 (24)	109 (21)	238 (23)
Beads	36 (6.8)	69 (13)	105 (10)
Missing[f]	2 (0.38)	1 (0.19)	3 (0.28)

TABLE 6 Baseline summaries: data collected at enrolment visit (*continued*)

Clinical variable	Antibiotic		Total
	IV (*N* = 527[a]), *n* (%)	PO (*N* = 527[a]), *n* (%)	(*N* = 1054[a]), *n* (%)
Antibiotics added to the cement during the operation	**n = *165***	**n = *178***	**n = *343***
Gentamicin	86 (52)	99 (56)	185 (54)
Vancomycin	29 (18)	31 (17)	60 (17)
Tobramycin	5 (3.0)	12 (6.7)	17 (5.0)
Other[g]	34 (21)	30 (17)	64 (19)
Missing[h]	11 (6.7)	6 (3.4)	17 (5.0)
Comorbidities[b,i]			
Diabetes	107 (20)	98 (19)	205 (19)
Renal failure	11 (2.1)	11 (2.1)	22 (2.1)
Ischaemic heart disease	43 (8.2)	45 (8.5)	88 (8.4)
Peripheral vascular disease	31 (5.9)	32 (6.1)	63 (6.0)
Previous stroke or TIA	19 (3.6)	22 (4.2)	41 (3.9)
Dementia	1 (0.19)	1 (0.19)	2 (0.19)
Immunosuppressing medication	28 (5.3)	17 (3.2)	45 (4.3)
HIV infection (if tested for)	1 (0.19)	3 (0.57)	4 (0.38)
Rheumatoid arthritis or systemic autoimmune disease	47 (8.9)	38 (7.2)	85 (8.1)
Current smoker	61 (12)	79 (15)	140 (13)
Malignancy (curent or diagnosed within the last 2 years)	17 (3.2)	17 (3.2)	34 (3.2)

HIV, human immunodeficiency virus; TIA, transient ischaemic attack.
a Number included in each summary, unless indicated otherwise.
b The inclusion categories are not mutually exclusive.
c This figure includes spinal and pelvic osteomyelitis.
d For one participant in the IV arm, infections were reported in both the upper and lower limbs. Therefore, the total number of infections in the IV arm add up to 528 instead of 527.
e One participant reported an infection in both the knee and hip.
f Information on antibiotic cement/beads used was unavailable for three participants.
g Of these, 52 participants received a combination of gentamicin and vancomycin, six received an aminoglycoside in combination with another agent and the antibiotic was not stated in six cases.
h Information on antibiotics used intraoperatively was unavailable for 17 participants.
i Of note, when a specific comorbidity was not indicated for a participant, this participant was assumed to not suffer from this comorbidity.

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TABLE 7 Baseline summaries: histology and microbiology data and infection status

Symptom or sign	Antibiotic		Total
	IV (*n* = 527)[a]	PO (*n* = 527)[a]	(*n* = 1054)[a]
Deep tissue histology result[b]			
Infected	266 (50.47)	277 (52.56)	543 (51.52)
Equivocal	13 (2.47)	17 (3.23)	30 (2.85)
Uninfected	31 (5.88)	32 (6.07)	63 (5.98)
Not done	212 (40.23)	197 (37.38)	409 (38.80)
Missing[c]	5 (0.95)	4 (0.76)	9 (0.85)
Deep tissue microbiology result[b]			
≥ 2 samples positive with the same organism	357 (67.74)	338 (64.14)	695 (65.94)
≥ 2 samples taken but only 1 sample positive with a given pathogenic organism	20 (3.80)	32 (6.07)	52 (4.93)
Only 1 sample taken which is positive for a pathogenic organism via closed biopsy	25 (4.74)	30 (5.69)	55 (5.22)
Culture negative	77 (14.61)	78 (14.80)	155 (14.71)
≥ 2 samples taken but only 1 sample positive with a given non-pathogenic organism	21 (3.98)	25 (4.74)	46 (4.36)
Not done[d]	22 (4.17)	20 (3.80)	42 (3.98)
Missing[c]	5 (0.95)	4 (0.76)	9 (0.85)
Results from the deep tissue microbiology (when available)	**(n = *500*)**	**(n = *503*)**	**(n = *1003*)**
S. aureus present[b]	196 (39.20)	182 (36.18)	378 (37.69)
Coagulase-negative *Staphylococcus* present[b]	137 (27.40)	135 (26.84)	272 (27.12)
Streptococcus species present[b]	72 (14.40)	73 (14.51)	145 (14.46)
Pseudomonas species present[b]	28 (5.60)	23 (4.57)	51 (5.08)
Other Gram-negative organism(s) present[b]	84 (16.80)	84 (16.70)	168 (16.75)
Infection status at present[b]			
Definite infection	478 (90.70)	476 (90.32)	954 (90.51)
Probable infection	13 (2.47)	10 (1.90)	23 (2.18)
Possible infection	30 (5.69)	27 (5.12)	57 (5.41)
Infection status unclear	6 (1.14)	13 (2.47)	19 (1.80)
Missing[e]	0 (0.00)	1 (0.19)	1 (0.09)

a Number included in each summary, unless indicated otherwise.
b Frequency and percentages are displayed.
c Day 42 CRFs were not received for eight randomised participants. The relevant fields were not completed for one further participant who withdrew consent soon after randomisation.
d These figures include participants who did not have surgical intervention.
e No baseline infection data were available for one participant (OV2019), who was consented in error and withdrawn immediately after randomisation.

Compliance

Treatment compliance

Compliance with the randomised strategy, including early exit, are secondary end points and are summarised in the results section.

Withdrawals and protocol violations

Withdrawals and losses to follow-up

Out of the 1054 randomised participants, 42 (3.98%) were reported as withdrawn or lost to follow-up. Follow-up for these participants ceased for the following reasons:

- participant withdrew from study, $n = 14$
- participant lost/did not attend scheduled clinic visits and was no longer contactable, $n = 12$
- patient had died, $n = 16$.

An additional seven deaths were reported within the acceptable range for the day 365 follow-up. The final follow-up for these participants is not considered missing. These deaths are reported in *Serious adverse events*.

Additional information on withdrawals and losses to follow-up by treatment arm can be found in the CONSORT statement. End-point data are available for three of these participants.

Protocol violations/deviations

The trial team are not aware of any protocol violations to date. The following 19 protocol deviations occurred:

- One participant who lacked capacity to provide personal informed consent was recruited in error. The participant was immediately withdrawn from further study related activity and all subsequent data were recorded as missing.
- One participant was recruited despite having had staphylococcal bacteraemia within the 30 days prior to randomisation. The participant had completed the course of therapy for bacteraemia by the time he was recruited to the trial. He was retained in the trial despite this deviation from the protocol.
- One participant was randomised on two separate occasions, once in the pilot study and once in the multicentre study. This patient was withdrawn from further study-related activity following realisation of the error and all subsequent data were recorded as missing.
- Eight participants (four in each arm) were discontinued early from their randomised strategy without an appropriate explanation. In all cases, a change to the prescription arose either as a result of an administrative error or on the advice of a clinician who was not involved with the OVIVA trial.
- Seven patients randomised to PO therapy switched to their randomised strategy beyond the 7 days allowed from start of treatment episode. The median delay in IV to PO switch from the start of the treatment episode in these patients was 12 days (range 10–19 days).
- One participant randomised to IV therapy started their IV treatment 8 days after the start of the treatment episode.

Blinding

Blinding was not applicable to the study; participants, clinical staff and the trial team were not blinded to the randomised intervention.

The independent end-point review committee was blinded: end points were assessed based on patient notes provided by trial sites, which were subsequently redacted by the trial staff at Oxford. Only one incident of unblinding was reported (OV1053). This unblinding was accidental and occurred as a result of inadequate redaction of notes. No other issues were reported by the blinded reviews.

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Primary analyses

Analysis using multiple imputation utilising all randomised participants

The frequency and proportions of participants experiencing primary end points (i.e. definitive treatment failures as identified by the independent end-point review committee), as well as those for whom the end-point data were missing because of participants withdrawing from the trial or being lost to follow-up prior to the 1-year post randomisation assessment, are shown in *Table 8*. This summary includes all randomised participants.

The results from the primary analysis and the supporting analyses are displayed graphically in *Figure 2*. The non-inferiority margin of 7.5% is indicated by the dashed line.

TABLE 8 Definite treatment failures

Analysis	Number (rate) of definitive treatment failures, *n* (%)		Risk difference (90% CI)
	IV antibiotic	PO antibiotic	
ITT population (all randomised participants, $N = 1054$)[a]	74 (14.04) [Missing:[b] 21 (3.98)]	67 (12.71) [Missing:[b] 18 (3.42)]	–1.38% (–4.94% to 2.19%)[c]
MITT subset (all participants with available outcome data, $N = 1015$)[c]	74 (14.62)	67 (13.16)	–1.46% (–5.03% to 2.11%)
All randomised participants, assuming no definite treatment failures for those with missing outcome data ($N = 1054$)[d]	74 (14.04)	67 (12.71)	–1.33% (–4.78% to 2.12%)
PP population ($N = 909$)[e]	69 (15.58)	61 (13.09)	–2.49% (–6.31% to 1.34%)

a Number of participants included: IV, $n = 527$; PO, $n = 527$.
b The number of participants with missing outcomes is 39, as opposed to 42, which is the number of participants without a final trial assessment. This is because three participants without a final trial assessment did have definitive treatment failure early in the trial, and end-point data are, therefore, available for them.
c This risk difference was calculated using multiple imputation to account for missing data.
d Number of participants included: IV, $n = 506$; PO, $n = 509$.
e Number of participants included: IV, $n = 443$; PO, $n = 466$.

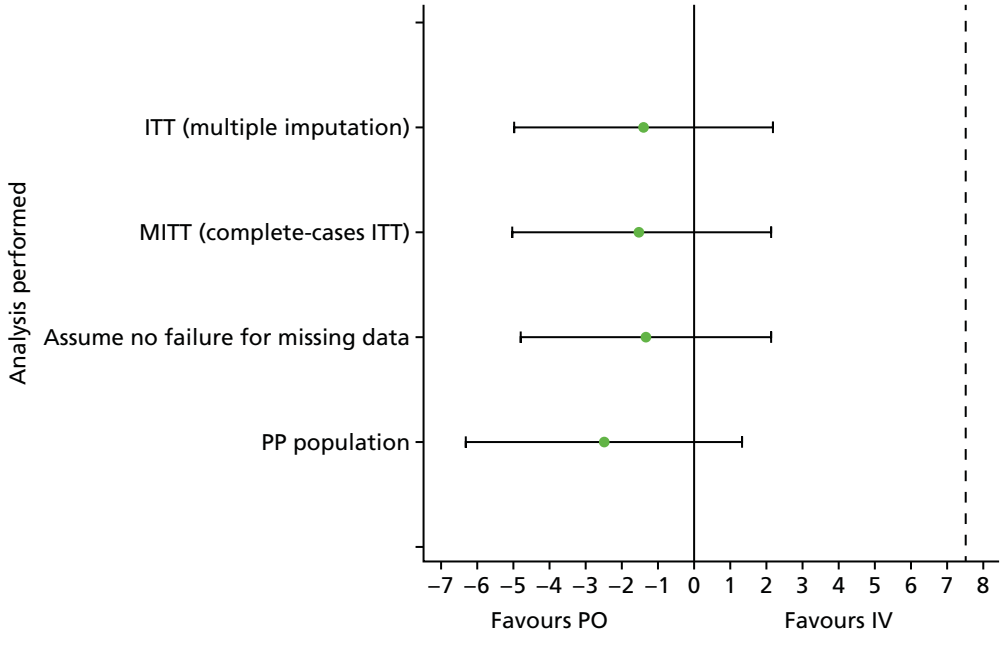


FIGURE 2 Forest plot of risk differences (95% CI) by analyses performed (PO vs. IV).

Adjusted logistic regression model

The model uses the occurrence of definite treatment failure as adjudicated by the blinded end-point review committee as the outcome and adjusts for randomised strategy, age, comorbidity (when sufficient observations are available), infecting pathogen and baseline surgical procedure.

The baseline surgical procedures have been categorised as follows:

1. chronic osteomyelitis debrided, no current implant or device
2. discitis/spinal osteomyelitis/epidural abscess debrided
3. chronic osteomyelitis as above but not debrided, or discitis/spinal osteomyelitis/epidural abscess but not debrided
4. implant or device present and retained [i.e. debridement, antibiotics and implant retention (DAIR)]
5. removal of orthopaedic device for infection
6. prosthetic joint implant removed
7. prosthetic joint implant, one-stage revision
8. the OVIVA trial infection criteria not met.

When participants fall into more than one category, they were assigned to the lowest numeric category in the above list. Categories with very low counts were combined with the next (lower) category.

All randomised participants are included in this model by using multiple imputation for missing outcome data. Insufficient incidence of comorbidities were observed for dementia and HIV (human immunodeficiency virus) infection. Infecting pathogen and baseline surgical procedure were categorised as defined in the section on primary end points.

There was no evidence of effect of the randomised strategy on the odds of experiencing a definitive treatment failure during the trial follow-up. The quantile regression models are adjusted for covariates. The covariate adjustment aims to separate the effect of the randomised intervention from other factors that may also have an influence on the odds of participants experiencing a definitive treatment failure during the trial follow-up. Low numbers may have been included in some levels of the categorical explanatory variables; the coefficients therefore have low power and should be interpreted cautiously.

Diagnostic checks demonstrated that the model has limited predictive ability (pseudo-$R^2 = 4\%$). However, the main purpose of the model was to obtain an average treatment effect, rather than to obtain accurate predictions for individual participants, and adequate goodness of fit was demonstrated when comparing the average predicted and observed probabilities of treatment failures in either arm. Lowess plots demonstrated linear relationships between the independent variables and the predictors. Investigation of the residuals showed some departure from normality; the majority of the residuals, except those at either end of the range of linear predictions, seemed independent from predicted values.

Time-to-event modelling

To assess any potential bias in the post-randomisation surveillance, which would present as a delay in time to meeting an end point in one randomised group or loss to follow-up or death without an event, a time-to-event analysis was performed.

This analysis focused on the timing of definitive treatment failures and was not adjusted for baseline characteristics. Six participants were withdrawn immediately after randomisation. They are therefore not included in the following summaries.

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The data entered under the 'date of review' for the day 365 assessment were used as the date at which the follow-up was censored for participants who did not experience a definitive treatment failure and who were not lost to follow-up. In some instances, these reviews were performed retrospectively, and the data entered reflect the timing of the review instead of the date at which data for the relevant participants were reviewed (i.e. a date within the follow-up window for the day 365 visit). Therefore, the time from randomisation to the final assessment was capped at 420 days.

There was no evidence to suggest that the hazard ratio between the treatment arms was statistically significantly different from 1. This suggests that there was no post-randomisation surveillance bias between the trial arms.

The Kaplan Meier curves in *Figure 3* show the definitive treatment failure-free time-to-event rates. Again, there does not seem to be any evidence to suggest that the time to definitive treatment failure differed between trial arms.

The test for the proportional hazards assumption, as well as log-log plots, indicate that the proportional hazards assumption is met (for the majority of the plot, i.e. the time where the majority of treatment failures occur).

Adjustment of *p*-values for multiple testing

There was no multiple testing, as only a single primary outcome was considered. All additional analyses were undertaken with an intention to further inform the results from the primary analysis. Therefore, significance levels used were 0.05, and 95% CIs were reported.

The DMC reviewed interim summaries and a formal interim analysis; however, it was expected that the DMC would only recommend early stopping if there was a very significantly worse outcome in the PO antibiotic group compared with the IV group (i.e. guided by the Haybittle–Peto stopping boundary). Therefore, the significance level used to determine early termination of the trial is very low (i.e. 0.001) and no formal adjustment of the *p*-value for the final analysis was considered necessary.

Missing data

Missing data were taken into account in the primary analysis, based on the ITT population, using multiple imputation. This was described in detail in the statistical analysis plan (see *Appendix 1*).

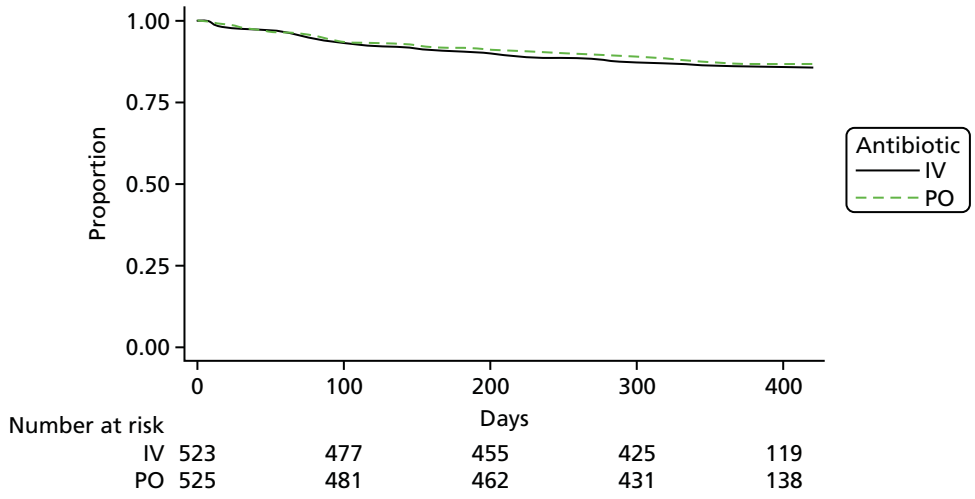


FIGURE 3 Kaplan–Meier curves for time to treatment failure by randomised strategy.

The multiple imputation and the MITT (complete-cases ITT) analyses make the assumption that data are missing at random. The sensitivity analysis looks at the impact of informatively missing data, assuming that data are missing not at random.

In addition to the assumptions made in the above supporting analyses (i.e. assuming no definitive failures for all participants with missing end-point data), this sensitivity analysis considers two extreme missing not at random assumptions (best-case/worst-case scenarios).

The first missing not at random sensitivity analysis makes the assumption that all participants with missing end-point data in the PO arm had a definitive treatment failure, while those with missing end-point data in the IV arm did not have a definitive treatment failure.

The second missing not at random sensitivity analysis makes the assumption that all participants with missing end-point data in the PO arm had no definitive treatment failure, while those with missing end-point data in the IV arm had a definitive treatment failure.

The sensitivity analyses did not alter the results from the primary trial analysis and, therefore, did not change the overall conclusions of the trial (i.e. that the non-inferiority criteria were met). Therefore, the trial results are robust to missing data.

Prespecified subgroup analysis

All subgroup analyses are based on the MITT population. Subgroup analyses for definite/probable/possible infection at baseline are repeated for the PP population.

Odds ratios were obtained from logistic regression models using definitive treatment failure as the dependent variable, and treatment allocation, the relevant subgroup as well as the interaction term as the only covariates.

The number of treatment failures by treatment arm observed in some of the subgroups were low. Therefore, some of the interaction effects may not be very robust (as indicated by wide CIs) or cannot be included in the plots.

Figure 4 summarises all subgroup analyses, showing the point estimates of the odds ratios, the 95% CIs and the numbers included in the analyses.

Based on the analysis, there was no evidence to suggest a statistically significant difference in the odds of treatment failure between the treatment arms. Odds ratios of > 1 favour IV therapy (i.e. indicate that the odds of experiencing a treatment failure in the PO arm were higher than the odds in the IV arm), whereas odds ratios of < 1 favour PO therapy.

Prespecified subgroup analysis considering infection subgroups at randomisation

Subgroup analysis of definite versus probable/possible infection at baseline

Modified intention-to-treat analysis analysis (complete-cases intention to treat)

A total of 1015 participants were included in this subgroup analysis.

The odds ratio of definitive treatment failures (PO vs. IV) in those with definitive infection at baseline was approximately 0.91, and the odds ratio for those with probable or possible infection was 0.56. *Figure 4* shows that the CIs for both odds ratios cross 1. The results for the probable/possible infection subgroup shows a lot of uncertainty owing to the small numbers included into this analysis.

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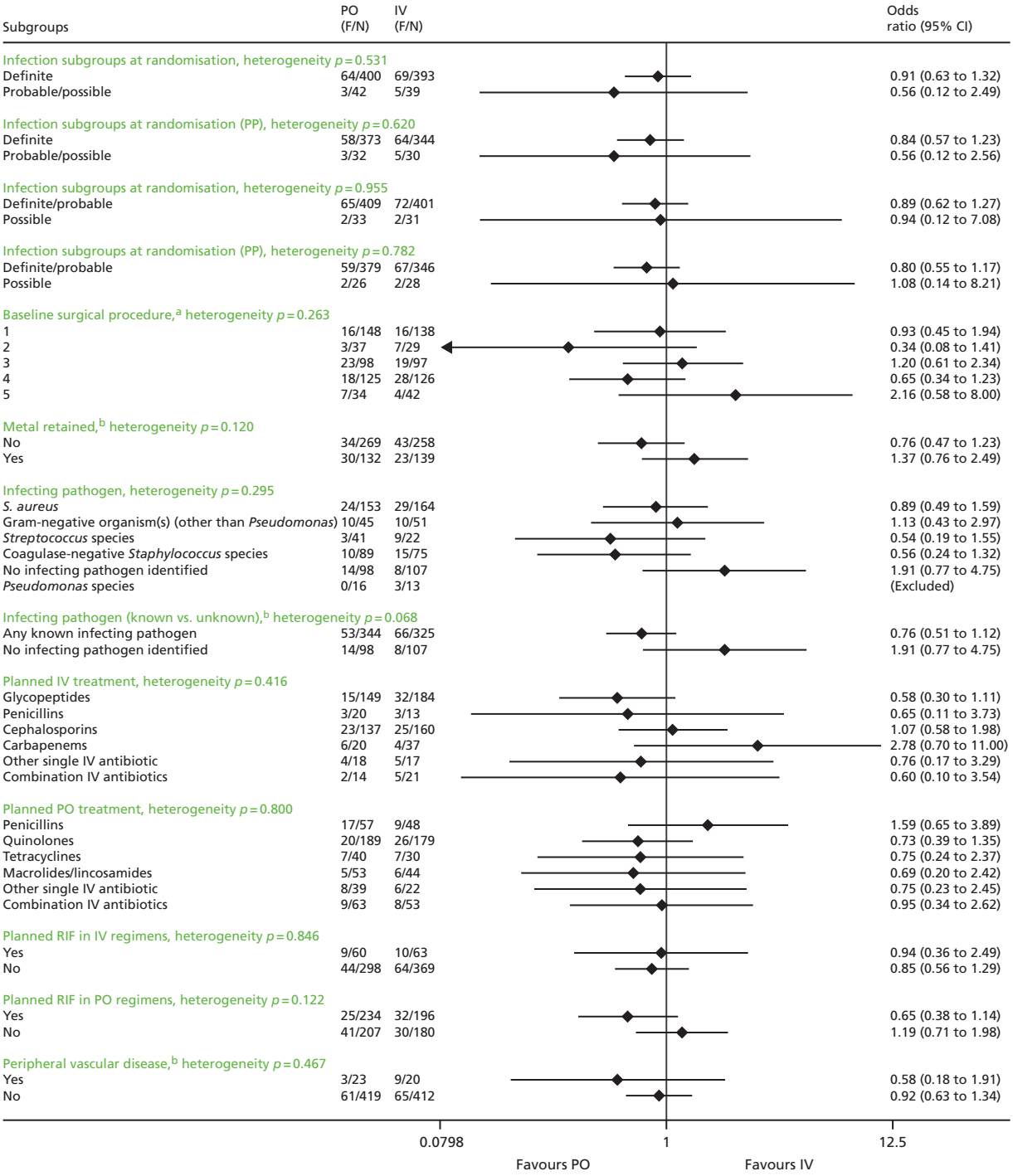


FIGURE 4 Forest plot of OR (95% CI) for subgroup analyses (PO vs. IV). a, Baseline surgical procedure 1 (chronic osteomyelitis debrided, no current implant or device or discitis/spinal osteomyelitis/epidural abscess debrided), baseline surgical procedure 2 (chronic osteomyelitis as above, but not debrided or discitis/spinal osteomyelitis/epidural abscess but not debrided), baseline surgical procedure 3 [implant or device present and retained (i.e. DAIR)], baseline surgical procedure 4 (removal of orthopaedic device for infection or prosthetic joint implant removed) and baseline surgical procedure 5 (prosthetic joint implant, one-stage revision); b, ad hoc subgroup analyses. F/N, Failure/no failure.

The overall interaction heterogeneity *p*-value is 0.531, indicating that there is no statistically significant difference in the treatment effect between the subgroups.

Per-protocol analysis

A total of 909 participants were included in this subgroup analysis.

The odds ratio of definitive treatment failures (PO vs. IV) in those with definitive infection at baseline was approximately 0.84, and the odds ratio for those with probable or possible infection was 0.56. CIs for both odds ratios cross 1. The results for the probable/possible infection subgroup shows a lot of uncertainty owing to the small numbers included into this analysis.

The overall interaction heterogeneity *p*-value is 0.612, indicating that there is no evidence that the interaction between randomised treatment and the subgroups is statistically significantly different from 1.

Subgroup analysis of definite/probable versus possible infection at baseline

Modified intention-to-treat analysis analysis (complete-cases intention to treat)

Data for 1015 participants are included in this subgroup analysis.

The odds ratio of definitive treatment failures (PO vs. IV) in those with definitive or probable infection at baseline was approximately 0.89, and the odds ratio for those with possible infection was 0.94. CIs for both odds ratios cross 1. The results for the probable/possible infection subgroup shows a lot of uncertainty owing to the small numbers included into this analysis.

The overall interaction heterogeneity *p*-value is 0.955, indicating that there is no evidence that the interaction between randomised treatment and the subgroups is statistically significantly different from 1.

Per-protocol analysis

Data for 909 participants are included in this subgroup analysis.

The odds ratio of definitive treatment failures (PO vs. IV) in those with definitive or probable infection at baseline was approximately 0.80, and the odds ratio for those with possible infection was 1.08. Results for the probable/possible infection subgroup shows a lot of uncertainty owing to the small numbers included into this analysis.

The overall interaction *p*-value is 0.782, indicating that there is no evidence that the interaction between randomised treatment and the subgroups is statistically significantly different from 1.

Prespecified subgroup analysis considering the baseline surgical procedure

Subgroup analysis was used to determine the consistency of treatment effects by the baseline surgical procedure. Information on the type of infection was collected at the enrolment of trial participants and categorised as follows:

- baseline surgical procedure 1 – chronic osteomyelitis debrided, no current implant or device or discitis/spinal osteomyelitis/epidural abscess debrided
- baseline surgical procedure 2 – chronic osteomyelitis as above, but not debrided or discitis/spinal osteomyelitis/epidural abscess but not debrided
- baseline surgical procedure 3 – implant or device present and retained (i.e. DAIR)
- baseline surgical procedure 4 – removal of orthopaedic device for infection or prosthetic joint implant removed
- baseline surgical procedure 5 – prosthetic joint implant, one-stage revision.

Results from a logistic regression model (ITT population) with the occurrence of the primary end point (i.e. definite treatment failure as adjudicated by the blinded end-point review committee) as the outcome, and the randomised treatment as well as the baseline surgical procedure (as a five-level categorical variable) and the interaction between randomised treatment and baseline surgical procedure as explanatory variables are presented.

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The interaction model does not indicate that any of the treatment/baseline surgical procedure interactions are likely to be significant.

The overall interaction heterogeneity *p*-value is 0.263, indicating that there is no evidence that the interaction between randomised treatment and the subgroups was statistically significantly different from 1.

In an additional post hoc subgroup analysis, restricted to metal retained versus not retained, we included participants from the following baseline surgical procedure categories:

- No metal retained –
  - chronic osteomyelitis debrided, no current implant or device
  - removal of orthopaedic device for infection
  - prosthetic joint implant removed.
- Metal retained –
  - implant or device present and retained (i.e. DAIR)
  - prosthetic joint implant, one-stage revision.

A total of 928 participants were included in this subgroup analysis.

The overall interaction heterogeneity *p*-value is 0.120, indicating that there is no evidence that the interaction between randomised treatment and the subgroups was statistically significantly different from 1.

Prespecified subgroup analysis considering the infecting pathogen

Subgroup analysis was used to determine the consistency of treatment effects by infecting pathogen.

Information on the following five infecting pathogens, and if there was no pathogen, was collected:

1. *S. aureus*
2. *Pseudomonas* species
3. Gram-negative organism(s) (other than *Pseudomonas*)
4. *Streptococcus* species
5. coagulase negative *Staphylococcus*
6. no infecting pathogen identified.

When evidence for more than one of the above pathogens was present on the deep tissue microbiology results taken prior to randomisation, they were assigned to the lowest numeric category in the above list. The infecting pathogen was therefore a single variable with six levels.

The above categories for the infecting pathogens were chosen as part of a pragmatic approach and included the main causative organism categories. It was felt that insufficient numbers of patients would be available for other infecting pathogens to enable meaningful statistical subgroup analysis.

A total of 1015 participants (i.e. all participants with valid end-point data) were included in this summary. Participants without an identified infecting pathogen were categorised as no infecting pathogen identified. As no failures occurred in the PO arm of the *Pseudomonas* spp. subgroup, an odds ratio could not be calculated for this group.

The overall interaction heterogeneity *p*-value was 0.295, indicating that there is no evidence that the interaction between randomised treatment and the subgroups was statistically significantly different from 1.

In the prespecified subgroup analysis, the point estimate suggests that IV therapy may confer an advantage for patients in whom no infecting pathogen was identified.

Therefore, an additional post hoc analysis was performed to investigate the odds of definitive treatment failure by treatment arm in participants with any pathogen compared with no pathogen identified.

The overall interaction heterogeneity *p*-value is 0.069, indicating that there is no evidence of an interaction between randomised treatment and whether or not the pathogen was known.

Table 9 summarises the use of antibiotics according to whether the pathogen was known or unknown. These data were available for 1011 participants.

This exploratory analysis demonstrates that in the IV arm, glycopeptides were the antibiotic category of choice when the infecting pathogen was not identified.

Prespecified subgroup analysis considering the intended and actual antibiotic choice

A subgroup analysis considered the clinician's specific antibiotic intentions, as recorded prior to randomisation, as a categorical variable. The antibiotic intentions were categorised into the following groups based on the intended drug (*Table 10*). The rationale for this was to ensure that participants should

TABLE 9 Categorisation of antibiotics used (excluding rifampicin)

	Antibiotics, *n* (%)				
	IV		PO		
Antibiotics used	Known pathogen (*N* = 391)	Unknown pathogen (*N* = 113)	Known pathogen (*N* = 396)	Unknown pathogen (*N* = 111)	Total (*N* = 1011), *n* (%)
Glycopeptides (IV) used	141 (36.06)	65 (57.52)	17 (4.29)	4 (3.60)	227 (22.45)
Penicillins (IV) used	27 (6.91)	7 (6.19)	5 (1.26)	3 (2.70)	42 (4.15)
Cephalosporins (IV) used	144 (36.83)	26 (23.01)	4 (1.01)	2 (1.80)	176 (17.41)
Carbapenems (IV) used	37 (9.46)	3 (2.65)	5 (1.26)	0 (0.00)	45 (4.45)
Other single IV antibiotic used	28 (7.16)	7 (6.19)	1 (0.25)	1 (0.90)	37 (3.66)
Combination IV antibiotics used	29 (7.42)	6 (5.31)	5 (1.26)	1 (0.90)	41 (4.06)
Penicillins (PO) used	7 (1.79)	1 (0.88)	61 (15.40)	20 (18.02)	89 (8.80)
Quinolones (PO) used	24 (6.14)	7 (6.19)	146 (36.87)	39 (35.14)	216 (21.36)
Tetracyclines (PO) used	1 (0.26)	3 (2.65)	44 (11.11)	11 (9.91)	59 (5.84)
Macrolides/lincosamide (PO) used	7 (1.79)	3 (2.65)	51 (12.88)	15 (13.51)	76 (7.52)
Other single PO antibiotic (PO) used	5 (1.28)	5 (4.42)	42 (10.61)	11 (9.91)	63 (6.23)
Combination PO antibiotics (PO) used	6 (1.53)	5 (4.42)	65 (16.41)	19 (17.12)	95 (9.40)

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TABLE 10 Categorisation of planned IV and PO treatments

Treatments	
Planned IV	**Planned PO**
1. Glycopeptides (i.e. teicoplanin/vancomycin)	1. Penicillins
2. Penicillins	2. Quinolones
3. Cephalosporins	3. Tetracyclines
4. Carbapenems	4. Macrolides/Lincosamide
5. Other single IV antibiotic	5. Other single PO antibiotic
6. Combination IV antibiotics	6. Combination PO antibiotics

have options for both IV therapy and PO therapy, thus demonstrating true equipoise from the infection specialist over the effectiveness of the two trial arms at the point of randomisation.

The results of the logistic regression models using the occurrence of the primary end points (i.e. definite treatment failure as adjudicated by the blinded end-point review committee) as the outcome, and the randomised treatment as well as the subcategory of the antibiotic intention and the interaction between the two variables are displayed below. Separate analyses are shown for the planned IV and planned PO treatments.

Intravenous and PO intentions were not documented for all participants, as it was not a requirement in the initial single-centre pilot study. Only those participants of the MITT population with available IV and PO plans were included into these analyses (913 participants).

Planned intravenous treatments

Of the 917 participants for whom relevant data were available, 380 were planned to receive glycopeptides if randomised to IV therapy. Of these, 216 were subsequently randomised to IV therapy and 164 were randomised to PO therapy. The asymmetry between the arms for missing data might suggest that these data fields were not reliably completed prior to randomisation.

The overall interaction heterogeneity *p*-value is 0.416, indicating that there is no evidence that the interaction between randomised treatment and the subgroups was statistically significantly different from 1.

Planned oral treatments

Of the 945 participants for whom relevant data were available, 131 were planned to receive penicillins if randomised to PO therapy. Of these, 57 were subsequently randomised to IV therapy and 74 were randomised to PO therapy. The asymmetry between the arms for missing data might suggest that these data fields were not reliably completed prior to randomisation.

The overall interaction *p*-value is 0.800, indicating that there is no evidence that the interaction between randomised treatment and the subgroups is statistically significantly different from 1.

Inclusion of rifampicin into the planned intravenous and oral choices

According to the available data, adjunctive rifampicin was included in the planned IV regimen in 142 partipants. Of these, 73 were subsequently randomised to IV therapy and 69 were randomised to PO therapy. The overall interaction heterogeneity *p*-value is 0.876, indicating that there was no evidence that the interaction between randomised treatment and the subgroups is statistically significantly different from 1.

Rifampicin was included in the planned PO regimen in 487 participants. Of these, 228 were subsequently randomised to IV therapy and 259 were randomised to PO therapy.

The overall interaction heterogeneity *p*-value is 0.122, indicating that there is no evidence that the interaction between randomised treatment and the subgroups was statistically significantly different from 1.

Treatment by peripheral vascular disease interaction

A final post hoc subgroup analysis looked at the effect of peripheral vascular disease as recorded at randomisation. This factor was identified as being associated with the outcome in the adjusted logistic regression analysis performed as part of the supporting analyses.

A total of 1015 participants (i.e. all participants with valid end-point data) were included in this summary.

The overall interaction heterogeneity *p*-value is 0.467, indicating that there was no evidence of an interaction between randomised treatment and whether or not peripheral vascular disease was present.

Adverse events and complications

Clostridium difficile

Summaries for episodes of *C. difficile* include all participants for whom at least one follow-up assessment was entered onto the database (*Table 11*).

Information on *C. difficile* was collected on the day 42 and day 120 CRFs. Day 42 forms were received for 1046 participants; all were included in this analysis. The day 120 form was received for a subset of these participants.

C. difficile data were missing for three participants: two in the IV arm and one in the PO arm. Two of these participants were withdrawn prior to their day 42 follow-up, and one died; therefore, the relevant information was not available for these participants (risk difference –0.8%, 95% CI –2.2% to 0.6%).

Using all participants with non-missing data (MITT population, $n = 1043$), there was no evidence of an association between randomised strategy and the occurrence of episodes of *C. difficile* (p-value = 0.298, using Fisher's exact test).

Serious adverse events

All reported and confirmed SAEs were included in the summaries reported in *Tables 12* and *13*.

Table 14 shows details for the SAEs reported in relation to randomisation.

TABLE 11 Summary of episodes of *C. difficile*

	Antibiotic		
Episode	IV ($n = 523$)	PO ($n = 523$)	Total ($n = 1046$)
Episode of *C. difficile*[a]	9 (1.72)	5 (0.96)	14 (1.34)

a Frequency and percentages are displayed.

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TABLE 12 Summary of patients with at least one recorded SAE and the number of reported SAEs per participant

	Antibiotic		
SAEs	IV ($n = 527$)	PO ($n = 527$)	Total ($n = 1046$)
SAE reported[a]	146 (27.70)	138 (26.19)	284 (26.94)
Number of SAEs reported[a]			
0	381 (72.30)	389 (73.81)	770 (73.06)
1	109 (20.68)	89 (16.89)	198 (18.79)
2	20 (3.80)	29 (5.50)	49 (4.65)
3	9 (1.71)	7 (1.33)	16 (1.52)
4	4 (0.76)	10 (1.90)	14 (1.33)
5	1 (0.19)	2 (0.38)	3 (0.28)
6	2 (0.38)	1 (0.19)	3 (0.28)
11	1 (0.19)	0 (0.00)	1 (0.09)

a Frequency and percentages are displayed.

TABLE 13 Summary of SAE information

	Antibiotic		
SAE information	IV ($n = 220$)	PO ($n = 224$)	Total ($n = 444$)
Timing of SAE onset from randomisation (in weeks)[a]	18 (4, 36), (0, 57)	16 (4, 35), (0, 56)	17 (4, 35), (0, 57)
SAE expected[a]			
Yes[b]	220 (100.00%)	224 (100.00%)	444 (100.00%)
SAE related to randomised intervention[a]			
No	218 (99.09%)	220 (98.21%)	438 (98.65%)
Yes	2 (0.91%)	4 (1.79%)	6 (1.35%)
SAE outcome[a]			
Resolved	154 (70.00%)	172 (76.79%)	326 (73.42%)
Ongoing[c]	10 (4.55%)	19 (8.48%)	29 (6.53%)
Resolved with sequelae	39 (17.73%)	27 (12.05%)	66 (14.86%)
Death	17 (7.73%)	6 (2.68%)	23 (5.18%)
SAE severity[a]			
Mild	56 (25.45%)	43 (19.20%)	99 (22.30%)
Moderate	119 (54.09%)	123 (54.91%)	242 (54.50%)
Severe	45 (20.45%)	58 (25.89%)	103 (23.20%)

a Frequency and percentages are displayed.
b There were no SAEs that were unexpected in accordance with the protocol definition.
c A total of 29 SAEs are marked as 'ongoing'. Of these, 12 were related to underlying chronic medical conditions (diabetic foot ulcers, $n = 6$; neoplasms, $n = 3$; rheumatoid arthritis, $n = 1$; ischaemic heart disease, $n = 1$; pressure ulcers in spina bifida, $n = 1$) and 12 episodes were eventually resolved following definitive treatment (deep-vein thrombosis, $n = 2$; RTA with fracture, $n = 1$; wound issues/recurrent dislocations leading eventually to surgery, $n = 9$). One SAE was still ongoing beyond the 1-year follow-up. Four SAEs were likely to have resolved by the time of discharge and were probably misclassified.

TABLE 14 Summary of SAE information for events related to the randomisation

ID number	Randomised treatment	Date of		SAE description as documented on the trial database	Outcome	Timing (weeks)
		Randomisation	SAE onset			
2113	PO	22 October 2013	30 October 2013	Admitted with nausea and vomiting. Had brief break from PO ciprofloxacin, which was then restarted	Resolved	1
2386	PO	1 July 2014	6 July 2014	Diarrhoea, nausea, vomiting and exhaustion associated with (liquid) PO antibiotics. Admitted for symptomatic therapy and switched to IV ceftriaxone	Resolved	0
2664[a]	PO	1 May 2015	24 June 2015	Left arm swelling investigated for midline infection; no infection or line complication found	Resolved	7
2694[b]	IV	11 June 2015	16 August 2015	Reaction to doxycycline: burning lower leg and blisters on feet. Widespread pruritus	Resolved with sequelae	9
2701[c]	IV	17 June 2015	26 June 2015	Severe oesophagitis thought to be attributable to PO antibiotics	Resolved	1
2796	PO	18 September 2015	22 September 2015	Participant had an unplanned admission as a result of intolerance of PO antibiotics. Symptoms were loose stools and a reduction in the effectiveness of the participant's methadone	Resolved	0

ID, identification.
a This participant exited early from their randomised strategy and received IV treatment.
b This SAE occurred during follow-up treatment (i.e. after completion of the randomised strategy).
c This participant received adjunctive PO therapy to which the SAE was ascribed.

The frequency of line complications

The following summaries refer primarily to participants randomised to the IV strategy; therefore, no statistical tests were performed (*Table 15*).

Information on line complications was collected on the day 42 and day 120 CRFs. Day 42 forms were received for 1046 participants and these are all included in *Table 15*. The day 120 form was received for a subset of these participants.

Information on line complications was missing for three participants: two in the IV arm and one in the PO arm. Two of these participants were withdrawn prior to their day 42 follow-up, and one died; therefore, the relevant information is not available for these participants.

Five line complications were reported in the PO arm of the trial. Of these, four related to participants who exited early from their allocated treatment strategy and were treated with IV therapy. One further line complication in the PO arm arose in relation to a planned second stage procedure, which took place after the completion of the 6 weeks' randomised strategy.

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TABLE 15 Summary of line complications

Line complications	Antibiotic		
	IV (*n* = 523)	PO (*n* = 523)	Total (*n* = 1046[a])
IV line details[b]			
Not present	64 (12.24)	489 (93.50)	553 (52.87)
PICC	450 (86.04)	30 (5.74)[c]	480 (45.89)
Hickman	5 (0.96)	1 (0.19)	6 (0.57)
Other[d]	2 (0.38)	2 (0.38)	4 (0.38)
Missing	2 (0.38)	1 (0.19)	3 (0.29)
Line complications[b]	49 (9.37)	5 (0.96)	54 (5.16)
Nature of line complications[b]	***(n = 49)***	***(n = 5[e])***	***(n = 54)***
Mechanical failure	24 (48.98)	3 (60.00)	27 (50.00)
Thrombophlebitis/thrombosis	13 (26.53)	1 (20.00)	14 (25.93)
Infection	12 (24.49)	1 (20.00)	13 (24.07)
Line removed as result of line complications[b]	***(n = 49)***	***(n = 5[e])***	***(n = 54)***
Yes	42 (85.71)	4 (80.00)	46 (85.19)
Replacement of line after removal	***(n = 42)***	***(n = 4)***	***(n = 46)***
Yes	18 (42.86)	4 (100.00)	22 (47.83)

PICC, peripherally inserted central catheter.
a Number of day 42 forms received.
b Frequency and percentages are displayed.
c The majority of these participants were early exits from their randomised strategy.
d The 'other' IV lines consisted of three peripheral cannulas, and one particant had an IV line for haemodialysis.
e Five incidences of line complications were reported in the PO arm of the trial. Four of these line complications occurred within the initial 6 weeks of treatment in participants who had exited early from their allocated PO strategy and were using IV treatments. The remaining line complication occurred beyond the initial 6 weeks of treatment.

Early termination of the planned 6-week strategy

Information on early termination from the allocated treatment strategy was collected on the day 42 and day 120 CRFs.

A total of 1046 participants had at least one of these forms available, and they are included in the following summaries (*Table 16*).

Information on early exits was missing for three participants. Two of these were withdrawn prior to their day 42 follow-up and one died; therefore, the relevant information was not available for these participants.

Pearson's chi-squared test (H_0: no association between treatment and early exit) suggests that there was evidence of an association between randomised treatment arm and early exit from the allocated strategy ($p = 0.006$).

Quality of life evaluated by the EuroQol-5 Dimensions, three-level version questionnaire

The EQ-5D-3L index ranges from –0.594 to 1, with higher values indicating better health states and zero indicating a health state equivalent to death.

TABLE 16 Early termination from allocated strategy by treatment arm

Reasons for early exit from allocated treatment strategy[a]	Antibiotic		Total
	IV [99/523 (18.93%)]	PO [67/523 (12.81%)]	[166/1046 (15.87%)]
Intolerance	26 (26.26)	23 (34.33)	49 (29.52)
Patient preference	19 (19.19)	5 (7.46)	24 (14.46)
Difficulties with IV access or administration	41 (41.41)	0 (0.00)	41 (24.70)
Intercurrent illness	2 (2.02)	8 (11.94)	10 (6.02)
Due to possible or probable recurrence[b]	1 (1.01)	15 (22.39)	16 (9.64)
Good clinical response	1 (1.01)	0 (0.00)	1 (0.60)
Other[c]	9 (9.09)	15 (22.39)	24 (14.46)
Reason not available	0 (0.00)	1 (1.49)	1 (0.60)

a Frequency and percentages are displayed.
b The participant in the IV arm was found to have a definitive treatment failure and their treatment was discontinued in preparation for further surgery. A total of 11 out of 15 participants in the PO arm were found to have a definitive failure, the remaining four did not have a definitive failure. In all cases, the participant was either switched to IV therapy, because of concern about possible therapeutic failure, or antimicrobials were stopped in preparation for surgery.
c Other reasons for early exit include:
- prescription changed by a clinician who was not involved in the OVIVA study (four PO and four IV participants)
- infection status was unclear and the clinicians decided that the participants did not need prolonged antibiotics (four PO and three IV participants)
- no PO option was available (six PO participants)
- early exit as clinician required particular antibiotic regimen to cover possibility of exotic organism (one IV participant)
- early exit because of poor compliance on PO medication (one PO participant)
- early exit linked to death (one IV participant).

The EQ-5D VAS ranges from 0 to 100, with higher values indicating better health states.

The results for the quantile regression on the EQ-5D-3L index and VAS showed no evidence of an effect of randomised strategy on the median outcome at any of the follow-up time points.

The quantile regression models were adjusted for a number of covariates, as outlined in the statistical analysis plan. The covariate adjustment aimed to separate the effect of the randomised intervention from other factors which may also have an influence on the EQ-5D-3L and EQ-5D VAS at follow-up.

Similarly, there was no evidence of an effect of randomised strategy on the median OHS outcomes at any follow-up time point. However, there was evidence to suggest that the randomised strategy has a statistically significant effect on the median outcome of the OKS at both the day 120 and day 365 follow-up in favour of PO therapy.

The quantile regression models were adjusted for a number of covariates, as outlined in the statistical analysis plan. The covariate adjustment aimed to separate the effect of the randomised intervention from other factors that may also have had an influence on the OHS and OKS at follow-up.

Adherence to oral medication

The MEMS was used in a subset of sites (Oxford University Hospitals, Guy's and St. Thomas' Hospitals, Royal Free London and Royal National Orthopaedic Hospital). MEMS caps were returned by 63 participants allocated to the PO arm. Compliance with PO therapy at 42 days according to MEMS data ranged from 45% to 100%.

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Antibacterial agents used for treatment

This section presents data on the antibiotic regimens received by participants during the first 42 days of the trial.

Data for 1044 participants were available for these summaries (*Table 17*). No antibiotic data were available for five trial participants and, for an additional five participants, insufficient antibiotic information was available to categorise their antibiotic regimen.

The categories in this table were not mutually exclusive; participants could fall into more than one category. A total of 145 participants fell into two antibiotic categories, three participants fell into three categories and one participant fell into four categories.

All participants in the PO arm who received IV antibiotics were early exits from their randomised strategy. All participants in the IV arm who received PO antibiotics were early exits from their randomised strategy or were on adjunctive PO therapy.

Figure 5 shows the proportion of participants on IV antibiotic therapy on each day from the start of treatment episode through to day 60, by treatment arm. As expected according to the trial protocol, the figure shows a marked decline in IV use around day 7 in the PO arm and around day 42 in the IV arm. Participants who were randomised to PO therapy but were receiving IV therapy after day 7 represent either early exits from strategy, permissible short-term IV therapy for concomittant illness or, in seven cases, protocol deviation. Two further apparent protocol deviations were likely to be a result of data entry error.

The number of patients continuing long-term antibiotic treatment (after 6 weeks) and time to permanent discontinuation of all antibiotic treatment (defined as the first day when antibiotics are not taken for the next 14 days) are displayed in *Table 18* and *Figure 6*. Antibiotic use was capped at 400 days when use was recoded beyond that period.

Using the Wilcoxon rank-sum test, there was no evidence of effect of randomised strategy on the median long-term use of antibiotics between the treatment arms ($p = 0.628$).

TABLE 17 Overview of actual antibiotic regimens

	Antibiotic		
Antibiotic regimen[a]	IV ($n = 521$)	PO ($n = 523$)	Total ($n = 1044$)
Glycopeptides (IV) used	214 (41.07)	22 (4.21)	236 (22.61)
Penicillins (IV) used	38 (7.29)	11 (2.10)	49 (4.69)
Cephalosporins (IV) used	173 (33.21)	8 (1.53)	181 (17.34)
Carbapenems (IV) used	41 (7.87)	5 (0.96)	46 (4.41)
Other single IV antibiotic used	35 (6.72)	2 (0.38)	37 (3.54)
Combination IV antibiotics used	35 (6.72)	6 (1.15)	41 (3.93)
Penicillins (PO) used	8 (1.54)	83 (15.87)	91 (8.72)
Quinolones (PO) used	33 (6.33)	191 (36.52)	224 (21.46)
Tetracyclines (PO) used	4 (0.77)	57 (10.90)	61 (5.84)
Macrolides/lincosamide (PO) used	10 (1.92)	68 (13.00)	78 (7.47)
Other single PO antibiotic used	10 (1.92)	54 (10.33)	64 (6.13)
Combination PO antibiotics used	13 (2.50)	87 (16.63)	100 (9.58)

a Frequency and percentages are displayed.

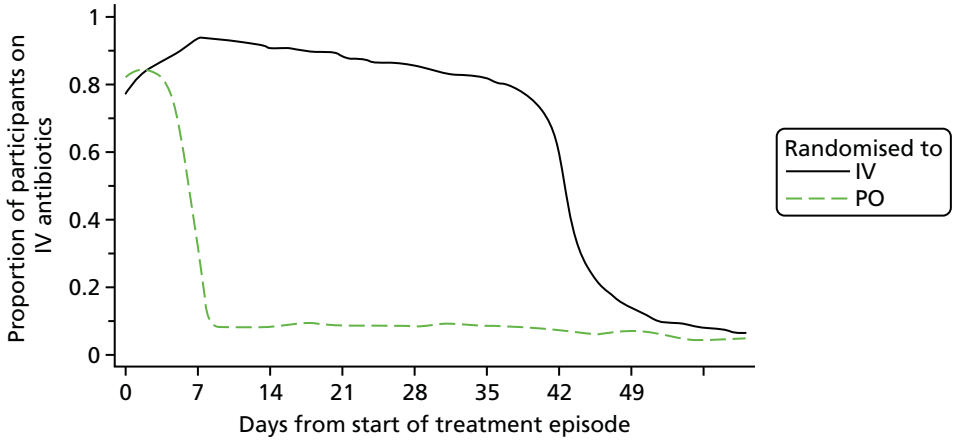


FIGURE 5 Proportion of participants on IV antibiotics from start of treatment episode through to day 60.

TABLE 18 Long-term use of antibiotics

Long-term use	Antibiotic		
	IV ($n = 523$)	PO ($n = 526$)	Total ($n = 1049$)
Antibiotic treatment continued beyond 6 weeks[a]			
No	139 (26.58)	125 (23.76)	264 (25.17)
Yes	384 (73.42)	401 (76.24)	785 (74.83)
Duration of antibiotic use[b]	78 (42–99) (1–400)	71 (43–94) (2–400)	76 (42–96) (1–400)

a Frequency and percentages are displayed.
b Median, interquartile range and range are displayed.

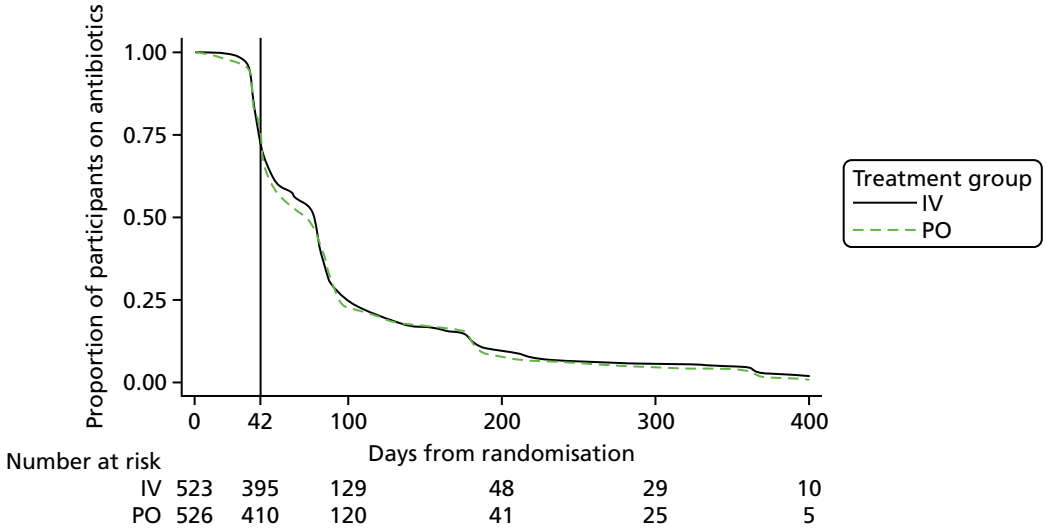


FIGURE 6 Time to permanent discontinuation of antibiotics.

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Agreement between intended and received antibiotics

This section presents agreements between the planned PO and IV antibiotics as stated prior to randomisation and actual antibiotic administered. Included in the summaries are participants for whom both the intended and actual antibiotic choices were available (*Table 19*). For one participant, the information provided was insufficient for categorisation.

Summaries are categorised as follows.

- Full match: received their randomised strategy and remained within the intended antibiotic group.
- Partial match: received their randomised strategy but deviated from the intended antibiotic group.
- No match: received < 50% of planned therapy within randomised strategy.

Note that the definition for the 'no match' category is different from that in the approved statistical analysis plan (version 2.0). Originally, this category was defined as 'early exit from randomised strategy'. The updated definition was felt to be more accurate and clinically relevant.

Duration of primary hospital stay

Time from randomisation to discharge is summarised in *Figure 7*. This summary excludes participants who were treated as outpatients (length of stay of zero) and those who died during their initial hospital stay. Note that readmission post discharge was recorded as a SAE and represented a secondary end point.

TABLE 19 Compliance with intended antibiotics as stated prior to randomisation

	Antibiotic		
Compliance[a]	IV ($n = 521$)	PO ($n = 523$)	Total ($n = 1044$)
Complete match	370 (71.02)	374 (71.51)	744 (71.26)
Partial match	68 (13.05)	90 (17.21)	158 (15.13)
No match	83 (15.93)	58 (11.09)	141 (13.51)
Missing[b]	0 (0.00)	1 (0.19)	1 (0.10)

a Frequency and percentages are displayed.
b For one participant, insufficient data had been provided to perform the matching.

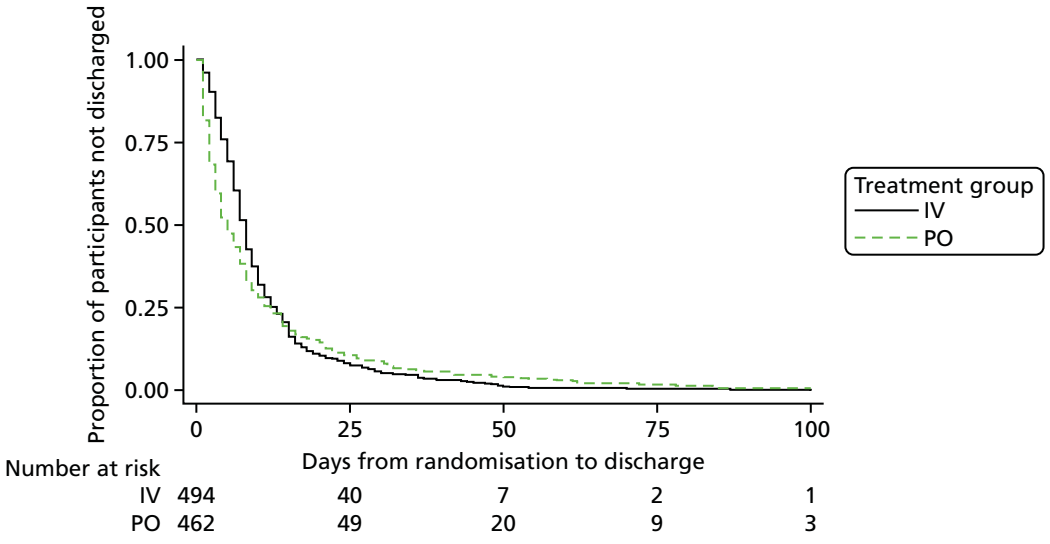


FIGURE 7 Time from randomisation to discharge.

Using the Wilcoxon rank-sum test, there is sufficient evidence to suggest a difference in the median time from randomisation to discharge between the treatment arms ($p < 0.001$).

Results of health economics analysis

Results from the trial indicate that PO antibiotics are non-inferior to IV antibiotics. Results are presented for complete cases as well as using the ITT population, for which missing values were replaced using imputation methods.

Missing data

The effects of missing data were explored using both mean and multiple imputation. Missing cost values were replaced at the aggregate total cost level using both mean imputation and multiple imputation. Missing quality-of-life data were replaced at utility score level at each EQ-5D-3L follow-up point using multiple imputation.

Resource use

Only a small proportion of patients had missing resource use data (IV arm, $n = 12$; PO arm, $n = 14$). *Table 20* shows data, for any indication, from incident admission through to 1 year of follow-up for the mean number of antibiotic prescriptions, antibiotic duration in days, mean number of inpatient admissions, the mean length of stay as inpatient and the total number of days that a patient received IV therapy. The antibiotic duration sums the duration of all antibiotic use, including simultaneous use. The IV duration includes the length of IV episodes for which an IV line was needed to administer IV antibiotics (including more than one IV antibiotic taken at the same time as another).

There were no statistically significant differences between arms for antibiotic prescriptions and duration, number of inpatient stays or total inpatient duration over 1 year. However, there was a statistically significant difference in the mean number of days' IV therapy was received. On average, the total number of days that IV therapy was received was 34.62 days longer in the IV arm than in the PO arm. *Table 21* presents the mean costs in both arms for unadjusted complete cases.

For unadjusted complete cases, the total mean non-surgical cost was £13,275 in the IV arm compared with £10,549 in the PO arm. The observed difference in mean total cost between arms was £2727, a statistically significant result. The mean cost differences for antibiotics and IV costs were also statistically significant, but there was no statistically significant difference in inpatient costs between the IV and PO arm over 1 year.

TABLE 20 Resource use per participant (complete case)

	Antibiotic					
	IV		PO			
Resource type	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	Difference	95% CI
Number of antibiotic prescriptions	6.70 (3.74)	515 (97.7)	6.43 (3.93)	513 (97.3)	0.276	–0.19 to 0.74
Antibiotic duration (days)	189.8 (177.5)	515 (97.7)	185.6 (156.3)	513 (97.3)	4.18	–16.29 to 24.65
Number of inpatient admissions	1.83 (1.15)	515 (97.7)	1.82 (1.11)	513 (97.3)	0.01	–0.12 to 0.14
Inpatient duration (days)	26.22 (24.28)	515 (97.7)	26.35 (28.47)	513 (97.3)	–0.125	–3.36 to 3.11
Total number of days IV therapy was received	52.58 (40.37)	515 (97.7)	17.96 (33.52)	513 (97.3)	34.62	30.08 to 39.16

SD, standard deviation.

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TABLE 21 Unadjusted base-case costs (complete case)

	Antibiotics						
	IV		PO				
Cost category	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	Difference	95% CI	*p*-value
Antibiotics	£1992 (£2545)	515 (97.7)	£1207 (£2043)	513 (97.3)	£785	£502 to £1067	< 0.01
Inpatient stays	£7756 (£7183)	515 (97.7)	£7793 (£8420)	513 (97.3)	–£37	–£995 to 920	0.94
IV costs	£3527 (£2920)	515 (97.7)	£1548 (£1618)	513 (97.3)	£1979	£1690 to £2268	< 0.01
Total costs (excluding surgical costs)	£13,275 (£10,113)	515 (97.7)	£10,549 (10,371)	513 (97.3)	£2727	£1473 to £3980	< 0.01

SD, standard deviation.

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To explore the difference in costs between IV and PO antibiotics for a 42-day course, trial results were used to calculate the mean daily cost of all antibiotics in each arm. The mean cost of a 42-day (6-week) course of antibiotics (antibiotics only) was £997 [standard deviation (SD) £873] for IV antibiotics and £188 (SD £648) for PO antibiotics.

Health outcomes: quality-adjusted life-years

The proportion of available data for each EQ-5D-3L questionnaire is presented in *Table 22*. These values include zero utility scores after death for deceased participants.

The complete-case EQ-5D-3L questionnaire results at dimension level showed that, in all domains, there was a lower proportion of participants in levels 2 and 3 at the 365-day follow-up than earlier follow-ups. This indicated that there was improvement in all aspects of the EQ-5D-3L from mobility through to anxiety, and this was seen in both the IV and PO arms.

The data for mean EQ-5D-3L utilities at baseline and at 14, 42, 120 and 365 days, along with mean QALYs, showed that there were no statistically significant differences in mean utilities at any follow-up point or in mean QALYs. Results consider a zero utility score for patients who died during the trial.[29] The utilities in both arms improved at each follow-up point compared with the previous follow-up point. Available data percentages ranged from 73.6% at baseline to 54.3% at the 365-day follow-up.

TABLE 22 Proportion of participants with available EQ-5D-3L score data

	Antibiotic	
Time point	IV (%)	PO (%)
Baseline	73.2	73.6
14 days	58.4	58.6
6 weeks	69.4	71.0
4 months	59.2	58.1
12 months	57.1	54.3

Imputation results

Mean and multiple imputation was carried out for total costs and are presented in *Table 23*.

Results for both mean and multiple imputation were consistent with the results from the base-case complete-case analysis; the mean cost differences for mean and multiple imputations were £2735 and £2740, respectively, compared with £2727 for complete-case analysis. All of these results showed a statistically significant difference between arms. The results of the multiple imputation for QALYs show a difference of –0.007 between arms, compared with 0.023 for complete cases. Neither of these results were statistically significant.

Sensitivity analysis

The results of the sensitivity analysis were similar to the base-case results, with a difference in total costs between arms of £2617–2887, compared with £2727 in the complete-case results.

Cost-effectiveness

Mean costs were observed to be lower in the PO arm and mean QALYs were higher in the PO arm than the IV arm, suggesting that the strategy of treating bone and joint infections with PO antibiotics is a dominant strategy. However, there is uncertainty surrounding this result, which is explored further in the next section.

Uncertainty

Although the difference in costs between strategies was found to be statistically significant, there is uncertainty around the magnitude of this difference and we can be 95% confident that this difference is between £1488 and £3992. The difference between QALYs is not statistically significant and results suggest that we can be 95% confident that the real difference in total QALYs between treatment arms is between –0.045 and 0.031 and, therefore, favours neither strategy.

Figure 8 shows the cost-effectiveness plane with 1000 bootstrap samples of the ICER. It also shows a point estimate giving the mean differences in costs and QALYs between treatment arms. This figure also includes a line showing the £30,000 threshold currently used to assess cost-effectiveness by National Institute for Health and Care Excellence (NICE), and the lower and upper 95% CI from the bootstrap samples.[35] All bootstrap samples had a lower cost in the PO arm than the IV arm, and most (82.8%) of cost-effectiveness pairs are in the south-east quadrant. In this quadrant, lower costs and higher QALYs can be observed for the PO arm as compared with the IV arm, which makes a PO intervention dominant for these samples.[29] However, some samples fall into the south-west quadrant of the plane, where patients in the PO arm have fewer QALYs than patients in the IV arm. Similar to observed cost-effectiveness results, non-parametric bootstrapping also resulted in a negative ICER of –£108,500, indicating that the PO strategy was dominant,

TABLE 23 Mean and multiple imputation results

	Antibiotic (mean costs)			
Total costs	IV	PO	Difference (SE)	95% CI
Mean imputation results				
Total costs	£13,141 (SD £10,036)	£10,406 (SD £10,269)	£2735 (£625)	£1508 to £3963
Multiple imputation results				
Total costs	£13,274 (SE £446)	£10,534 (SE £453)	£2740 (£638)	£1488 to £3992
Total QALYs	0.537 (SE 0.013)	0.545 (SE 0.015)	–0.007 (0.019)	–0.05 to 0.03

SE, standard error.

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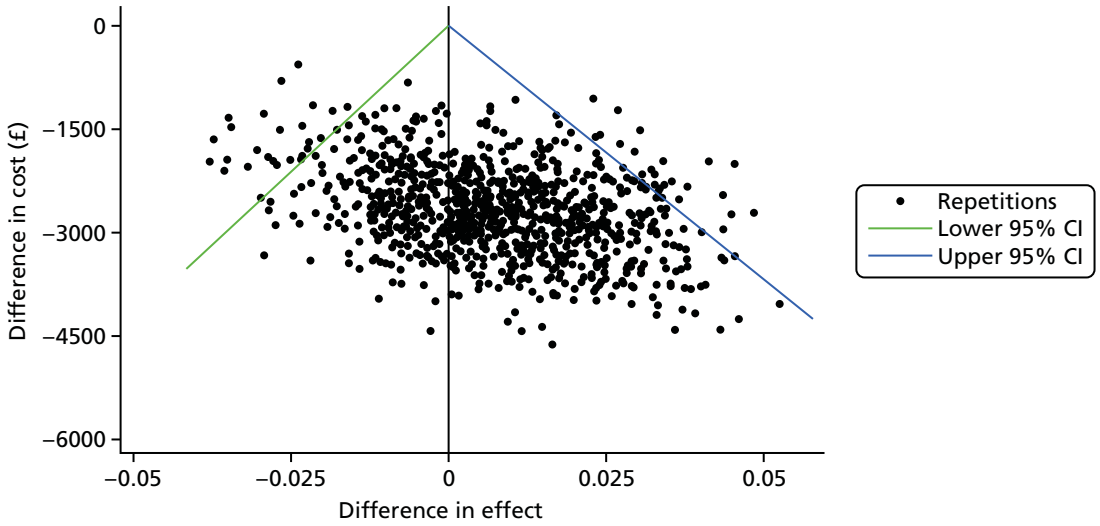


FIGURE 8 Cost-effectiveness plane. Reproduced with permission from McMeekin *et al.*[29] © 2019 McMeekin *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

with the 95% CI ranging from –£1,592,000 to £1,126,000. The mean cost difference was £2924 (standard error £1031) in favour of the PO strategy, and mean QALYs were 0.027 (standard error 0.031) in favour of the PO strategy. The lower 95% CI line indicates that there is a possibility that the true difference in QALYs may be in the south-west quadrant. When the IV intervention results in higher QALYs than the PO intervention, there is uncertainty that the PO arm dominates; 17.2% of the bootstrap samples fall in the south-west quadrant, where the IV strategy is less costly but also results in higher QALYs. The strategy of treating bone and joint infections with PO antibiotics is dominant in the lower limit of the 95% CI, and it is also dominant in the point estimate of the ICER and has an upper limit of £1,126,000 per QALY gained.

Chapter 4 Discussion

Some of the material in this chapter has previously been published in our description of the trial, reproduced from Li *et al.*[1] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Despite a widely held view that the successful management of bone and joint infection requires IV rather than PO antibiotics,[38–40] there is no evidence to suggest that PO antibiotic therapy results in worse outcomes. Nonetheless, there is significant variation in practice, with some centres advocating prolonged courses of IV therapy, some using short courses of IV therapy and others relying primarily on locally administered antibiotic agents.[41,42] Such lack of consensus demonstrates that the current trial addresses an important question and that the results are likely to influence practice. This is reflected in a study[43] in which 500 infectious diseases physicians were asked to prioritise more than 100 research questions relating to infection. Four out of the top five responses related to route of administration of antibiotics and the top two concerned orthopaedic infection specifically.

The aim of the trial was to determine whether or not PO antibiotic therapy is non-inferior to IV antibiotic therapy when used for the first 6 weeks in the treatment of bone and joint infection. All recruiting centres routinely used a 6-week course of IV therapy for some or all bone and joint infections as their standard care pathway.

The results of the OVIVA trial demonstrate that PO therapy, when used during the initial 6 weeks in the treatment in bone and joint infection, is non-inferior to IV therapy. This finding held true for the ITT analysis, the complete-case analysis (which excluded participants for whom no valid end-point data were available), the PP analysis (defined by participants who received at least 4 weeks of their allocated treatment strategy or who exited early owing to potential treatment failure) and for sensitivity analyses (which substituted missing primary end points with the most extreme possible outcomes).

A secondary analysis, which included 16 possible and probable treatment failures as composites with definitive treatment failure, also demonstrated non-inferiority of PO therapy as compared with IV therapy.

Predefined subgroup analyses focusing on diagnostic certainty at baseline, surgical procedure, bacterial pathogen, trial site and planned IV or PO antibiotic regimen at the time of randomisation showed no evidence of a differential effect of either treatment arm. Similarly, post hoc analyses relating to retention of metalware, peripheral vascular disease and culture-negative infection demonstrated no advantage of IV over PO therapy. For a pragmatic and unselective trial, with significant heterogeneity in the population under study, the findings from these subgroup analyses are reassuring and, overall, suggest that the results from this trial can reasonably be assumed to be broadly generalisable. However, none was sufficiently powered formally to compare outcomes following IV and PO therapy and, although we believe that we selected the most important subgroups for analysis, we cannot exclude the possibility that there are otherwise unidentified subgroups for whom IV (or PO) therapy may be superior.

Adverse events and complications

For the purposes of this trial, *C. difficile* diarrhoea and complications relating to IV access devices (or lines) were analysed as secondary end points rather than SAEs.

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As expected, line complications were significantly more common among participants randomised to IV therapy. Although the incidence was relatively modest, the mortality associated with line infection in particular has been reported at 12–25%.[44] Elimination of this risk by using PO therapy may therefore offer considerable advantage and, extrapolating from the presumed incidence data that we used to inform the design of the OVIVA trial, could avert 19–40 deaths annually in the UK.

The incidence of *C. difficile* diarrhoea and SAEs did not differ significantly between the treatment arms. A total of 23 patients died during the conduct of the study but none was considered related to the randomised strategy.

Patient-reported outcome measures

Data collection for the EQ-5D-3L was suboptimal. Although we cannot be certain that the missing data arose randomly, the trial showed no evidence that randomised strategy had any effect on the EQ-5D index at any time point.

The OHS and OKS were originally designed as assessment tools to indicate whether or not patients may have reached a threshold for joint replacement.[45,46] Although not necessarily directly applicable to the population included in this trial, they have been validated as research tools. We therefore collected the data as part of an assessment of functional outcome. For the OHS, the unadjusted scores indicated a difference between the trial arms at 120 and 365 days in favour of IV therapy, but in an adjusted quantile regression model there was insufficient evidence to suggest that the randomised strategy had a statistically significant effect on the median outcome at any time point. For the OKS, unadjusted scores indicated a difference between the trial arms at 120 and 365 days in favour of PO therapy, and the adjusted quantile regression model amplified this difference, which was statistically significant at both time points. A plausible biological explanation for this is lacking but it is possible that the difference between the adjusted and unadjusted estimates is attributable to the fact that only a small subgroup of the population is included in either the OHS or OKS sample.

There was clear evidence of improvement over time in all elements of the EQ-5D, and in the OHS and OKS, in both arms of the trial. This suggests that patients' mobility, self-care, activity level, pain, psychological status and joint function generally improved progressively following the start of treatment for their incident bone or joint infection.

Adherence to medication

At the outset of this trial, we were concerned that if PO therapy proved inferior to IV therapy, this might have arisen as a result of 'failure of compliance with oral therapy' rather than 'therapeutic failure of oral antibiotics'. To address this concern, we issued very clear guidance on the importance of adherence, both verbally and in writing, at the time of randomisation. We did not subsequently provide direct adherence support, such as text reminders, as this would be difficult to translate into routine practice.

Follow-on antibiotic therapy

The total duration of treatment, including follow-on therapy after the initial 6 weeks of treatment, is usually determined by a combination of factors such as the presence or absence of metalware, the organism isolated, the certainty with which all non-vital tissue has been excised and the availability of options for further surgical intervention should an infection recur. Previous studies have shown that timing of recurrence

of infection is commonly related to the cessation of antibiotic therapy.[47] In this open-label trial, we were concerned that clinicians might inadvertently (or deliberately) extend follow-on therapy for participants who had been randomised to the PO arm. Therefore, we analysed the total duration of therapy in all participants. The results demonstrated no evidence of prolongation of follow-on therapy in one or other arm of the trial. There were clear indicators that the proportion of participants remaining on therapy fell markedly at 6 weeks, 3 months, 6 months and 1 year. Although these time points reflect clinical practice, they probably represent digit preference rather than an evidence base governing total duration of therapy. It suggests that significant redundancy may be built into our current practice; if so, there could be considerable gains in terms of cost and antibiotic minimisation if optimal duration of therapy could be more clearly defined prospectively.

Health economics

As the results of the trial indicate that PO antibiotics are non-inferior to IV antibiotics, there is no possibility of incremental benefit in outcomes of one treatment over the other. Therefore, it was not considered necessary or useful to carry out a full economic evaluation. The results of the EQ-5D-3L questionnaires reflected the main trial outcome of definitive failures; there was no statistically significant difference in the QALYs between arms.[29] This was reinforced by post hoc regression of QALYs on 'definite failure', for which the indicator variable for failure was found to be statistically significant, confirming that the EQ-5D measure is sensitive to the end point. However, the end point was found not to differ between arms. The difference in costs between arms was £2740 using multiple imputation, indicating that the use of PO antibiotics to treat a bone or joint infection was significantly cheaper (when taking into account the cost of antibiotics, IV administration and inpatient stays over the course of 1 year) than the use of IV antibiotics. With PO antibiotics being non-inferior to IV administration, and the costs in the PO arm being significantly less than the IV arm during the trial, the results suggest that the PO arm was a dominant strategy.

However, there was uncertainty around these results. Although there was no statistical difference in the QALYs, and PO antibiotics were found to be non-inferior to IV antibiotics using the primary outcome, the uncertainty around the economic results was explored further. These results suggested that, although in 82.8% of the bootstrap sample the PO strategy is dominant, 17.2% of the samples indicated that the IV strategy would result in higher QALYs than the PO strategy and still at a higher cost. However, at the NICE willingness-to-pay threshold of £30,000 there was a 100% probability of the PO intervention being more cost-effective than the IV intervention.

Despite the economic burden of bone and joint infection, economic studies in this area are rare.[48] A cost-effectiveness study that compared exchange arthroplasty with debridement and prosthetic retention for infected total hip arthroplasty in the elderly found that retention and debridement improved quality-adjusted life expectancy and also increased costs in 65- and 80-year-old men and women over a lifetime.[49] The ICER ranged from US$500 for frail 80-year-old men to US$21,800 for 65-year-old women. Kapadia *et al.*[50] conducted an economic evaluation in which they explored using chlorhexidine cloths before total knee arthroplasty and reported that for 1000 patients having total knee arthroplasty, a net saving of US$2.1M occurred.[29] This study assumed an estimated cost of US$130,000 per revision owing to infection, with 22 patients in a cohort of 1000 without use of the cloth becoming infected and six infections in the cohort using the cloth. Two studies estimated revision costs for infected prosthetics: for infected hip arthroplasties, estimated costs were £22,000[51] and for infected knees, estimated costs were £30,000.[52] These costs included the revision surgery and subsequent inpatient stay.[29] A 2013 review summarised the economic literature in the treatment of periprosthetic joint infections, looking at prevention, treatment and surgical options.[53] Unlike the OVIVA trial, the treatment costs included the surgical costs of revision based on an estimated average cost of US$50,000 to US$60,000 per patient with an infected total hip arthroplasty.[48] None of these studies compared treatment costs of IV with PO antibiotics. The OVIVA trial estimated non-surgical costs over the year to be £13,274 for those treated with IV antibiotics and £10,534 for those treated with PO antibiotics.

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After imputation of missing values for resource use and health outcomes (QALYs), results remained consistent with those obtained from complete-case analysis. QALYs reflect the primary outcome of non-inferiority. Results from sensitivity analyses were also consistent with the complete-case and imputation results.

Strengths

The OVIVA trial was pragmatic in that it was fully embedded into usual care and, as far as possible, reflected standard practice in all respects other than randomisation of treatment strategy and data collection. No additional diagnostic investigations, trial-specific clinic visits or blood tests were required of the participants. This had the advantage of reducing the influence of possible differential observer effects by treatment arm.

The OVIVA trial was a large trial and clinically evaluable primary end-point data were available for 1015 participants representing 96.3% of those randomised. This was well within the 10% allowance in the sample size calculation for loss to follow-up.

Of the 39 participants lost to follow-up, only 14 (seven in each arm) withdrew consent to further involvement with the trial. This suggests that the study design and patient pathway were generally acceptable.

The primary end point was hard in that it was predefined by clinically relevant criteria as used in daily practice. When these criteria were not clearly fulfilled, a blinded end-point committee assessed potential treatment failures from clinical records redacted for personal identifiers and for any indication of the randomisation arm. The latter included redaction for all specifically named antibiotics, any reference to IV lines and any reference to line complications, side effects and use of MEMS containers.

Recruitment criteria were highly inclusive. The hypothesis behind the trail was based strictly on the pharmacokinetic principle that carefully selected PO antibiotics are as likely as IV antibiotics to achieve sufficiently high concentrations to effect eradication of infection. Such a principle is unlikely to be influenced by factors such as site of infection, retention of metal or causative organism. A more restrictive recruitment strategy, for example selecting only participants with *S. aureus* infection or primary arthroplasty, would have made the trial prohibitively long and would have limited the utility of the results. Although the inclusive recruitment criteria resulted in an heterogeneous study population, we believe that the advantages of generalisability outweigh the disadvantages of heterogeneity.

Weaknesses

The OVIVA trial was an open-label study. The decision to use this design was based on the two principles. First, exposure of patients to a placebo IV therapy for a period of up to 6 weeks would have posed unnecessary risks associated with the use of an intravascular access device and would, therefore, have been unethical. Second, owing to the number of different antibiotics required to provide optimal care for all patients randomised, it was not feasible to provide a matched placebo in every case. Although an open-label design leaves the trial open to bias, the primary end points were determined according to predefined criteria and an independent committee that was blinded to treatment allocation. This was achieved through redaction from case notes of any information that might have betrayed the treatment allocation (e.g. reference to IV access, OPAT, drug names, therapeutic drug monitoring). Primary end points were defined by objective clinical and microbiological criteria, assessment of which required attendance at, or admission to, hospital. Therefore, they were hard end points, the interpretation of which was unlikely to have been influenced by treatment allocation or other confounding factors.

The OVIVA trial was designed as a pragmatic trial that relied on routine care records as the primary source of data. There were no research-specific clinic visits and no research-specific investigations. When possible, and provided that the timings were commensurate with follow-up requirements of the trial, follow-up data were collected through direct patient contact at their routine clinical reviews. When this was not possible, the protocol allowed for telephone follow-up with the patient and the GP. Although primary end-point data were available for all except 39 participants, it is possible that some potential treatment failures were not identified. Although we think this unlikely, there is no reason to believe that unidentified losses influenced one arm more than the other.

Eligibility for recruitment to the trial was based on clinical criteria rather than diagnostic laboratory results. There are several reasons why we did not include histological or microbiological results as part of the inclusion criteria. First, approximately 15% of bone and joint infections diagnosed clinically are not confirmed microbiologically, for example, as a result of prior exposure to antibiotics or sampling error.[54] Nonetheless, such patients are commonly treated for infection diagnosed on clinical criteria alone. Second, the results of laboratory tests, particularly the histology results, are not always available within 7 days of sampling; had we relied on laboratory results as part of the inclusion criteria, many patients would have had to be excluded from this trial on account of this delay. Third, the pragmatic design of this trial gave due autonomy over clinical management to the surgeon or physician responsible for the patient. If, according to a research definition, infection was deemed not present, the trial could potentially have undermined a clinician's decision to treat an infection based on clinical criteria alone. Finally, in order to account for the possibility that uninfected patients were included, every case that failed to meet a strict prospective definition of infection at baseline was reviewed by an independent committee for a consensus decision on their infection status at the time of recruitment.

There are three circumstances in which an apparent deviation from the allocated treatment arm might have arisen.

First, participants were permitted IV therapy for up to 7 days following the start of planned curative therapy, regardless of their randomised strategy (in most instances, the 'start of planned curative therapy' was the date of definitive surgical intervention). The rationale for this was to allow patients to recover from the effects of anaesthesia before starting PO therapy and to allow sufficient time for microbiological results to inform the optimal choice of antimicrobial agent. The availability of microbiological results was not a requirement prior to randomisation but, because standard practice usually includes initial broad-spectrum empiric IV antibiotics while waiting for microbiology results, we felt that a requirement for immediate postoperative use of PO therapy might undermine clinical decision-making. Furthermore, operative findings were an important component of eligibility and, as a result, most patients were randomised in the postoperative period.

Second, for participants randomised to IV therapy, the use of adjunctive PO agents was permitted. This may at first seem counterintuitive in a study that aimed to compare IV with PO therapy, but is based on common practice outside the context of the trial. Examples include PO rifampicin, which is routinely used alongside IV therapy in the management of biofilm-associated staphylococcal disease and metronidazole, which is commonly used in polymicrobial osteomyelitis. To exclude patients allocated to the IV arm but who require adjunctive PO therapy would likely incur a bias in favour of PO therapy.

Third, participants randomised to the PO arm were allowed up to 5 days of IV therapy to allow for treatment of intercurrent illness or for short periods when, for unrelated reasons, PO therapy was not appropriate. It was not designed to be used as a rescue treatment for the bone infection under therapy and the protocol made this very clear. To withdraw participants on the grounds that they had an unrelated concomitant illness which, in the opinion of a physician independent of the trial, required IV therapy would have been considered unethical or discriminatory by some readers. Given that all patients had to have

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been prescribed at least 6 weeks of therapy for the incident bone infection, we believe that a short course of IV therapy in a small minority of patients is unlikely significantly to have influenced the results. To ensure transparency around both of these circumstances, all antibiotic use (including dose, route of administration and duration) was recorded from the day of randomisation through to 1-year follow-up.

There was considerable variation in the number of participants recruited at each site, with over half being recruited at just two centres. Both were tertiary referral specialist units, which consequently have high volumes of orthopaedic surgery and its associated complications. Therefore, it is unsurprising that these centres accrued a higher number of eligible patients than other centres. In addition, the single-centre pilot study contributed 228 participants at one of these sites. The asymmetry of recruiting between sites is unlikely to influence interpretation of the results and, in the 11 sites for which subgroup analysis was possible, there was no evidence of an interaction between randomised treatment strategy and study site.

Follow-up in this trial was for 1 year with the facility to obtain final clinical review data up to 420 days. The data points were made deliberately wide because the trial relied on routine clinic attendance to capture end points and adverse events. Had we included trial-specific clinics at more tightly defined time points, the trial may have been open to a greater influence of observer bias. Because follow-up was limited to 1 year, we cannot, of course, assume from our results that very late recurrences will be equally distributed between those who were randomised to IV and PO therapy. However, there is no biologically plausible reason to suggest otherwise and, given that the median total duration of therapy was around 11 weeks, we believe that there was unlikely to be an advantage of following up participants for longer than 1 year.

There are some important caveats relating to antibiotic therapy in orthopaedic surgery and are detailed below.

First, the effective management of bone and joint infection is critically dependent on effective surgical management. This may include careful and complete surgical debridement and excision, a meticulous sampling framework to optimise diagnostics in the microbiology and histopathology laboratories, and early vital soft tissue cover. Regardless of the route of administration, antibiotic therapy is likely to be ineffective without appropriate and adequate surgical intervention. Researchers involved in this trial were self-selected and are therefore likely to represent centres with surgical expertise specifically in the management of bone and joint infection.

Second, the antimicrobial agents used in this trial were chosen by specialists in clinical infection, with reference to bioavailability, tissue penetration and likely effectiveness against the known or presumed pathogen. It cannot be assumed that an antibiotic will be effective based simply on the reported susceptibility of the target organisms. This is particularly true for PO antibiotics for which a wide range of agents is available and for which oral bioavailability and dose are critical for efficacy.

Third, because adherence to therapy is plausibly better with supervised IV therapy than with self-administered PO therapy, participants in this trial were provided with written information explaining the importance of adherence. It is critical that, if the findings of this study are used to support a change in practice from routine use of IV to PO therapy, due consideration should be given to mechanisms to promote adherence.

Fourth, patients managed with long courses of IV therapy, commonly through an OPAT service, are likely to be more closely supervised than those on PO therapy during the first 6 weeks of treatment. Although the trial did not demonstrate any difference in time to treatment failure between the two arms, it may be that, because of their involvement in the trial, participants on PO therapy were more closely followed up than they might have been outside the context of a trial. Extrapolation of the results into routine practice should therefore take account of the need for adequate monitoring of patients after discharge.

Comparison with previous studies

There have been a limited number of studies on this topic. A Cochrane review,[15] which included data from five trials involving a total of 180 patients with chronic osteomyelitis, demonstrated no benefit of IV over PO antibiotic therapy, although the authors concluded that there was insufficient evidence to inform clinical practice. We believe that the OVIVA trial provides sufficient support for these findings to allow widespread adoption of PO therapy in this setting. Our results concur with The Infectious Diseases Society of America guideline on the management of prosthetic joint infections,[55] and a review by Fraimow,[56] which suggest that the use of highly bioavailable PO agents may be an appropriate alternative to IV therapy, provided that patient factors do not limit the drug's pharmacokinetic properties.

Implications for practice

Patient pathways

There is a clear professional mandate to ensure patient-centred treatment, including, when possible, limitation of hospital attendances, promotion of an independent life style and greater patient choice over their own treatment.[57] Such gains are less achievable with IV therapy than they are with PO therapy for the following reasons:

- Use of IV therapy results in a delay in discharge from hospital, most commonly while awaiting insertion of an IV access device and setting up OPAT. The median delay, quantified prospectively as part of the OVIVA trial, was 3 days for patients managed with IV therapy.
- Clinic visits, although not quantified in this trial, would almost certainly have been more numerous among those randomised to IV therapy than to PO therapy on account of therapeutic drug monitoring and line checks/manipulation.
- Patients on IV therapy after discharge from hospital, unless self-administering, may find it inconvenient to either arrange access in their own homes for a visiting nurse or to attend the hospital infusion centre on a regular basis, usually daily. Furthermore, the presence of a line may restrict social and sporting activities such as swimming, which patients may regard as important for their rehabilitation. Although we did not specifically collect qualitative data to assess patient preference or satisfaction, we contributed to a separate trial over the same period.[58] This study suggested that, for prolonged IV therapy, self-administration yielded significant cost savings, although patient preference was for home visits by a specialist nurse. The study did not compare preference for IV therapy with preference for PO therapy.
- Conversations with our patient and public involvement (PPI) representatives revealed that a potential further advantage of oral administration is the sense of control that patients feel over their own treatment, particularly on account of the ease, familiarity and portability of tablets, that they would not have had with IV therapy.

Patient safety

The use of IV lines pose risks that are not directly relevant to patients on PO therapy. For the purposes of this trial, line complications were recorded as secondary end points (rather than SAEs) and included line fracture or blockage, bleeding, thromboembolic events and line-related infection. Line-related infection carries with it a crude mortality estimate of up to 25%.[59] Around 10% of evaluable patients who were randomised to IV therapy for the OVIVA study suffered a line-related complication. This figure is either lower than or similar to other reports, although the populations involved are not directly comparable.[60,61] Nonetheless, we believe that almost all of these complications could have been avoided in participants managed with PO therapy.

Although we would not have expected line-related complications among those randomised to PO therapy, five such instances were recorded. In four of these participants, the line was placed following early exit from the randomised strategy (i.e. the participant was switched from PO to IV therapy during the intervention period) and, in one participant, the line complication occurred after completion of the intervention period.

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Cost

The acquisition cost of IV antibiotics is generally greater than that of PO therapy. In the OVIVA trial, the mean total drug cost for those randomised to IV therapy was almost £800 greater than PO therapy. IV therapy incurs additional costs relating to drug administration and prolonged hospitalisation. The mean non-surgical treatment costs over the year for patients randomised to IV therapy was approximately £2700 greater than that of patients randomised to PO therapy. Extrapolation based on the most conservative estimates used to inform the design of the OVIVA trial suggests a potential saving to the NHS of over £30M if PO rather than IV therapy becomes the standard of care in the early treatment of bone and joint infection across the UK.

Discussion with service users and PPI representatives suggested that the socioeconomic costs associated with IV therapy represent a significant burden. Time absent from work, child care and travel to hospital clinics were considered important. Additional hidden costs relating to delayed discharge, worry about complications, lack of social engagement, work absence and effects on family/social environment were all thought to be higher in those managed with IV therapy.

Antibiotic resistance

Antimicrobial stewardship activity has become a major priority in health care. PO therapy provides an opportunity for a reduction in use of broad-spectrum antibiotics. The global threat of antimicrobial resistance has been highlighted by the UK Chief Medical Officer as a very major risk to the NHS. Progress in limiting the overall exposure to broad-spectrum antibiotics will reduce this threat and limit the risks of health care associated infections such as *C. difficile*, methicillin-resistant *S. aureus* and carbapenemase-producing *Enterobacteriaceae*. This is of particular relevance to the treatment of orthopaedic infections, which commonly mandate an extended course of antibiotic therapy. Although not all PO antibiotics are narrow spectrum, it is easier to select targeted therapy with PO agents than it is with IV agents. The effective use of PO therapy in orthopaedic infection will help preserve the broad-spectrum IV antibiotic use for serious infections, particularly when therapeutic options are limited.

Implications and suggestions for research

1. Given the advantages of PO over IV therapy discussed, the findings of this trial suggest that it would be value to prospectively investigate its use in other conditions in which prolonged courses of IV therapy are thought to be necessary for optimal outcome. These include bacteraemia, endocarditis and meningitis. Although the incidence of these conditions is lower than that of bone and joint infection, there is still considerable potential for patient benefit, cost reduction and improved antimicrobial stewardship.
2. To further support patient safety, cost improvement and antimicrobial stewardship, additional work to define the optimal total duration of antibiotic therapy in bone and joint infection is necessary. Currently, there is considerable variation between centres and between clinicians, which suggests that there may be significant redundancy in antibiotic use. This almost certainly contributes to the risk of emerging resistance to antimicrobials, an issue that is high on the agenda of the Department of Health and Social Care and the medical community globally.
3. Effective antibiotic therapy requires the presence of therapeutic drug levels at the site of the infected tissue. This depends on both bioavailability and tissue penetration. Optimising antibiotic choice will require a programme of work that may include techniques such as microdialysis of tissue fluid at the site of deep surgical infection.
4. There is currently growing interest in the literature around environmental factors that might influence SSI rates. To limit the number of bone and joint infections arising as a complication of surgery, there is considerable scope to investigate simple perioperative interventions that could reduce the risk of surgical site infection in orthopaedics. Examples might include the influence of different patient-warming technologies during surgery, the effect of preoperative transfusion and choice of postoperative dressings.

Chapter 5 Conclusions

Despite its limitations, this trial is the largest study of its type addressing the question of route of administration of antibiotic therapy in bone and joint infection. Currently, the majority of centres that manage complex bone and joint infections routinely use a prolonged course of IV antibiotics in the early phase of therapy. The results of this trial suggest that this strategy has no advantage over PO therapy. In addition, use of PO therapy will allow clinicians to mitigate the risks associated with IV access devices normally used for long-term IV therapy. There was no significance difference in the incidence of *C. difficile* diarrhoea or SAEs.

For patients, PO therapy provides an opportunity for earlier discharge from hospital, autonomy and independence in managing their medications, and limitation of the risks associated with prolonged use of IV access devices. These advantages have to be weighed against the risk of poor adherence with unsupervised PO therapy. Although this did not appear to influence clinical outcome in the trial, adherence monitoring during the trial may have influenced the behaviour of a subset of participants.

The demonstration of non-inferiority of PO therapy provides an important opportunity for antimicrobial stewardship. Because the choice of PO agents is generally greater than that of IV agents, it seems likely that the results of this trial will facilitate much greater capacity for individualisation of therapy, thereby ensuring that the use of broad-spectrum agents can be better restricted to cases in which no alternatives exist. It provides an important opportunity to support the global fight against emerging antimicrobial resistance.

The results from the OVIVA trial could provide an opportunity for considerable cost savings. These arise primarily from the shorter period of hospitalisation, the drug costs and the resources associated with their administration. The health economic analyses in the OVIVA trial suggested that, on average, the non-surgical treatment costs over 1 year for patients randomised to PO therapy were approximately £2700 less than those of IV therapy.

Translation of the results from the OVIVA trial into clinical practice is likely to have important implications for patients, health-care practitioners in the field of orthopaedic infection and the health economy.

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Acknowledgements

The OVIVA trial was funded by the National Institute for Health Research (HTA project number 11/36/29).

The Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) co-ordinated the study via the Surgical Interventions Trials Unit and the trial sponsor was Oxford University Hospitals NHS Trust.

The authors greatly appreciate the considerable contributions of Neil French, Martin Llewelyn and Colette Smith as DMC members, and of David Beard and Cushla Cooper for their support through the CTU. The authors also acknowledge the valued input from Fraser Old (public patient representative), Alice Harin, Lorrayne Jefferies, Louise Spoors, Patrick Julier and all the members of the infectious diseases and orthopaedic departments at Oxford University Hospitals NHS Trust.

Our gratitude also to Brian Angus, Andrew Woodhouse, Tony Berendt, Parham Sendi, Ivor Byren and Hemant Pandit for their substantial intellectual input and advice throughout.

The authors would like to thank members of the United Kingdom Clinical Infection Research Group (UKCIRG), principal investigators and research staff across the 26 contributing sites. These included Gavin Barlow, Oliver Koch, Catherine Sargent, Caroline Barker, Jim Buckley, Aula Abbara, Tumena Corrah, Martin Williams, Rashmi Sharma, Achyut Guleri, Bijayendra Singh, Uli Schwabb, Jonathon Campion, Nick Nicolaou, Sentil Velayudhum, Michael Kelsey, Parvez Moondi, Ian Dos Remedios, Neena Bodasing, Julia Grieg, Stephen Mapham, Sophie Collier, Conor Bowman, Fiona Fitzgerald, Kim Cox, Jocelyn Marshall, Karen Bisnauthsing, Antonio Querol-Rubiera, Sam Stafford, Helen Reynolds, Marie Claire Hoyle, Parizade Raymode, Kareen Darnley, Angela Dunne, Claire Vallance, Deborah Bunne, Chris Herriott, James Calderwood, Elizabeth Saunders, Sue Brown, Natalia Waddington, Rebecca Houlihan, Louise Flintoff and Helen Sankey.

We are extremely grateful to the funding agency and to all patients who participated.

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Publications

Li HK, Scarborough M, Zambellas R, Cooper C, Rombach I, Walker AS, *et al.* Oral versus intravenous antibiotic treatment for bone and joint infections (OVIVA): study protocol for a randomised controlled trial. *Trials* 2015;**16**:583.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Please note exclusive use will be retained until the publication of major outputs. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Statistical analysis plan



Oral versus intravenous antibiotic treatment for bone and joint infections requiring prolonged antibiotic treatment: Multi-centre study

Statistical Analysis Plan

Version 2.0 - 03/12/2016

Based on version 2.0 - 01/05/2015 of protocol

	Name	Title/Role	Signature	Date
Author, approver	Ines Rombach	Trial Statistician		
Reviewer, approver	Sarah Walker	Senior statistician		
Approver	Matthew Scarborough	Chief Investigator		

RCS Surgical Intervention Trials Unit



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1. Introduction

This document details the proposed presentation and analysis for *the HTA-funded Multicentre Randomised Controlled Trial of Oral versus Intravenous Antibiotic Treatment for bone and joint infections requiring prolonged treatment (OVIVA)*. Any primary reporting of the OVIVA study should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 *Key personnel*

Trial statistician(s):

Ines Rombach (Surgical Intervention Trials Unit)

Chief Investigator:

Matthew Scarborough (Oxford University Hospitals)

Trial Manager:

Rhea Zambellas (Surgical Intervention Trials Unit)

Trial Physician:

Ho Kwong Li (Oxford University Hospitals)

DSMC Members:

Neil French, DMC chair, Professor of Infectious Disease, Liverpool University

Colette Smith, Lecturer in Biostatistics, UCL

Martin Llewelyn, Reader in Infectious Diseases and Therapeutics, Brighton and Sussex University

TSC Members:

Dr Graham Cooke, Consultant Infectious Disease and Senior Lecturer

Dr John Paul, Lead Public Health microbiologist, South East Region

Mr Fraser Old, retired

Ms Jennifer Bostock, Mental Health Act Commissioner for CQC

2. Changes from previous version of SAP

This is the second version of the statistical analysis plan, based on protocol version 2.0, 05th May 2015. Details on changes from previous versions are provided in section 13.

3. Background Information

3.1 *Objectives*

Primary Aim

To determine whether oral antibiotics are non-inferior to intravenous antibiotics for serious bone and joint infection judged by the percentage of patients experiencing definitive treatment failure during 1 year of follow up.

Secondary Aims

To compare the following endpoints according to treatment allocation;

1) SAEs, including death (i.e. all cause) according to treatment allocation.
2) line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line).
3) *Clostridium difficile* associated diarrhoea
4) "probable" and "possible" treatment failure as composites with definitive treatment failure (see endpoint definitions and analysis section for details).
5) early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason.
6) resource allocation using; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs.
7) Quality of life, as evaluated by EQ-5D-3L questionnaire
8) Oxford Hip and Knee Scores (where infection is in the hip or knee)
9) Adherence, as indicated by MEMS (see below) in a subset of participants.

3.2 *Study Design*

The current OVIVA trial is a multi-centre, open label, randomised non-inferiority two-arm pragmatic parallel group clinical trial (one year follow-up), in 1050 people with serious bone and joint infection.

Date of start of recruitment:	26/03/2012– start of main study 03/06/2010 – start of internal pilot
Date of end of recruitment*:	31/10/2015
Date of end follow-up*:	31/10/2016
Date of analysis*:	01/11/16 – 20/01/17
Target number of subjects:	1050 (approximately 525 per arm) including the pilot

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*Originally, recruitment to the OVIVA study was to conclude at the end of October 2014. Due to the initial recruitment being lower than expected, the trial was granted a no-cost extension. The above presented timelines take into account this extension.

Participating Centres (NHS Trusts) include:

Oxford University Hospitals NHS Trust; Guy's and St. Thomas' Hospitals NHS Foundation Trust; Royal Free London NHS Foundation Trust; Royal National Orthopaedic Hospital NHS Trust; Birmingham Heart of England NHS Foundation Trust; Royal Liverpool and Broadgreen University Hospitals NHS Trust; Cambridge University Hospitals NHS Foundation Trust; Leeds Teaching Hospital NHS Trust; Sheffield Teaching Hospitals NHS Foundation Trust; University Hospitals Bristol NHS Foundation Trust; Newcastle upon Tyne Hospitals NHS Foundation Trust; Hull and East Yorkshire Hospitals NHS Trust; Brighton and Sussex University Hospitals NHS Trust; Maidstone and Tunbridge Wells NHS Trust; Norfolk and Norwich University Hospitals NHS Foundation Trust; Northampton General Hospital NHS Trust; Northumbria Healthcare NHS Foundation Trust; Queen Elizabeth Hospital King's Lynn NHS Foundation Trust; University Hospital of North Staffordshire NHS Trust; Medway NHS Foundation Trust; Royal Cornwall Hospitals NHS Trust; NHS Tayside; NHS Lothian and NHS Greater Glasgow and Clyde; North West London Hospitals NHS Trust; Blackpool Teaching Hospitals NHS Foundation Trust; Calderdale & Huddersfield NHS Foundation Trust; Royal United Hospital Bath NHS Trust

3.3 *Eligibility*

Inclusion Criteria

1) A clinical syndrome comprising any of the following;
    a) localized pain
    b) localized erythema
    c) temperature >38.0ºC
    d) a discharging sinus or wound
2) willing and able to give informed consent
3) aged 18 years or above
4) the patient has received 7 days or less of intravenous therapy after an appropriate surgical intervention to treat bone or joint infection (regardless of pre-surgical antibiotics) or, if no surgical intervention is required, the patient has received 7 days or less of intravenous therapy after the start of the relevant clinical episode.
5) has a life expectancy > 1 year
6) has a bone and joint infection in one of the following categories;
    a) Native osteomyelitis (i.e., bone infection without metalwork) including haematogenous or contiguous osteomyelitis, and long bone, skull, foot or other foci
    b) Native joint sepsis treated by excision arthroplasty
    c) Prosthetic joint infection treated by debridement and retention, by one stage revision or by excision of the prosthetic joint (with or without planned re-implantation)
    d) Orthopaedic device or bone-graft infection treated by debridement and retention, or by debridement and removal
    e) Spinal infection including discitis, osteomyelitis and/or epidural abscess.

Exclusion Criteria

1) Staphylococcus aureus bacteraemia on presentation or within the last 1 month

2) bacterial endocarditis on presentation or within the last month (NB there are no study mandated investigations. Participants are not required to have echocardiograms, blood cultures, or any other investigations to exclude endocarditis in the absence of a clinical indication)
3) Any other concomitant infection which, in the opinion of the clinician responsible for the patient, required a prolonged intravenous course of antibiotics (e.g. mediastinal infection or central nervous system infection)
4) Mild osteomyelitis, defined as osteomyelitis which, in the opinion of the clinical investigator, would not usually require a 6 week course of intravenous antibiotics
5) An infection for which there are no suitable antibiotic choices to permit randomization between the two arms of the trial (for instance, where organisms are only sensitive to intravenous antibiotics, which occurred in <5% of patients during recruitment for our pilot study)
6) Previous enrolment in the trial
7) Septic shock or systemic features requiring intravenous antibiotics in the opinion of the treating clinician (the patient may be re-evaluated if these features resolve)
8) The patient is unlikely to comply with trial requirements following randomization (including specific requirement for PO or IV course) in the opinion of the investigator
9) There is clinical, histological or microbiological evidence of mycobacterial, fungal, parasitic or viral aetiology
10) The patient is receiving an investigational medical product as part of another clinical trial

The use of antibiotic-loaded cement in spacers or beads at the site of infection will not be an exclusion criterion, but will be recorded in baseline data. Pregnancy, renal failure and liver failure will not be exclusion criteria provided suitable antibiotic choices can be identified.

3.4 *Treatment Interventions*

Eligible patients will be randomized (1:1) to complete the first 6 weeks of antibiotic therapy with the selected course of either IV or PO antibiotic therapy. The selection of individual antibiotics within the allocated strategy (i.e. PO or IV antibiotics) will depend on microbiological assessments, the side effect profile of different antibiotics, patient preferences and epidemiological factors suggesting the likelihood of antibiotic-resistance organisms. Treatment decisions will be left to the clinician caring for the patient, but should remain within the randomized strategy (i.e., either PO or IV antibiotics). If there is no suitable empirical oral antibiotic choice for an individual patient while waiting for culture results, the clinician responsible for the patient may prolong IV antibiotic therapy without withdrawing the patient from the PO antibiotic strategy, provided IV prescribing does not continue beyond 7 days after the beginning of the episode (i.e. after an appropriate surgical procedure or the start of antibiotic prescribing for the clinical episode being treated).

If a participant requires surgery, or experiences an intercurrent illness causing vomiting, inability to swallow, or any other concern about absorption of oral medication, then IV antibiotic therapy may be substituted for a brief period without withdrawing the patient from the randomized strategy. This period should be no longer than 5 days if the patient is to remain “according to protocol”. Note that even if IV antibiotic prescribing exceeds the limits set in the PO strategy, the patient will still contribute to “intention to treat” analysis, and study follow up should therefore continue.

Adjunctive oral antibiotics will be allowed at any stage in the IV group (e.g. oral rifampicin may be added to intravenous antibiotics).

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However, if at any point continuing in the randomized strategy (IV or PO) is no longer compatible with good clinical care, the study participant will discontinue the randomized treatment. Study related follow up will continue unless the participant declines this, and the participant will be included in intention to treat analysis. Appropriate reasons for discontinuing the allocated treatment would be that no suitable medication can be selected within the allocated strategy because of adverse reactions, contraindications and susceptibility testing results. Failure to maintain intravenous access is an appropriate reason for discontinuing IV antibiotics and switching to PO antibiotics to complete the first 6 weeks. A wound discharge, superficial erythema or other clinical sign related to infection or resolution of infection is not an appropriate indication for changing PO to IV or vice versa, since there is equipoise regarding efficacy.

If a patient is to be withdrawn from the randomized strategy, this should be discussed with the study CI, the trial physician or another delegate of the CI beforehand. Changing the antibiotic used while remaining within the allocated strategy need not be discussed, but should be done by a clinician with appropriate training in managing infection. Patients who are withdrawn from the allocated strategy should nevertheless continue to be followed up using the trial protocol.

Patients who are withdrawn from their allocated treatment will be included in "intention to treat" analysis of efficacy, but not in the "according to protocol" analysis. Patients who meet a study endpoint may remain in the PO strategy for purposes of selecting their ongoing antibiotic treatment, since there is equipoise regarding the relative efficacy of PO and IV antibiotic treatment.

Dose adjustments based on renal or hepatic function, drug interactions or other factors will be made by the clinician according to drug labelling information, the British National Formulary and local pharmacy guidelines.

The dose and antibiotics used will be recorded in the CRF at scheduled reviews.

3.5 *Sample Size*

Original sample size calculation:

In the Oxford pilot, 10 participants experienced a primary endpoint among the first *197* randomizations. Based on a 5% event rate, we will require 950 evaluable participants for sufficient power (at one-sided alpha=0.05 and power=90%) to determine that the PO strategy is non-inferior to the IV strategy, defined as the upper 90% confidence limit for the difference being less than a 5% absolute increase in event rate (i.e. an increase to 10%). To compensate for participants being lost to follow up (allow for approximately 10%), and to ensure that the "according to protocol" analysis retains reasonable power, we will aim to recruit 1050 participants.

Updated sample size calculation:

After the interim analysis, the sample size calculation for the OVIVA trial was updated as follows:

In the Oxford pilot, 10 participants experienced a primary endpoint among the first *197* randomizations. Based on an anticipated 5% event rate, we estimated that 950 evaluable participants (uplifted to 1050 to account for loss to follow up and to allow for per protocol analyses) would be necessary (at one-sided alpha=0.05 and power=90%) to determine that the PO strategy is non-inferior to the IV strategy, defined as the upper 90% confidence limit for the difference being less than a 5% absolute increase in event rate (i.e. a relative increase of 100%). Following an interim analysis in March 2015, pooled data from the multicentre trial over a 1 year follow-up period demonstrated that the true event rate is plausibly closer to 12.5%. In response to this finding, we have adjusted the non-inferiority margin to 7.5% (i.e. a relative increase of 60%) with explicit agreement from the DMC. Using 90% power and a one-sided alpha of 0.05, a minimum of 744

participants would be required, allowing for a 10% loss to follow-up. As the final control group failure rate remains unknown, and to optimise the potential utility of subgroup analyses, the recruitment target will remain 1050.

3.6 *Strategies for achieving adequate recruitment*

During the trial, regular telephone conferences and a trial specific website were implemented to enable sites to share good practice and to allow for discussion around recruitment rates and protocol adherence. In addition, the trial has been publicised and additional sites have been included. Monthly updates of recruitment numbers by site are circulated and personal contact with PIs and their research teams are maintained where necessary.

3.7 *Randomisation*

Trial participants will be randomised (1:1) to either the PO or IV treatment strategy using a randomisation list with varying block sizes stratified by site.
The randomisation schedule, consisting of one list per site, will be prepared by the trial statistician and transferred to the OCTO programming team using secure methods of transfer. The lists will be held securely by the trial statistician and the OCTO programming team. OCTO will provide the randomisation database and randomisation services support.
The trial statistician conducts regular checks to ensure the randomisation is working as expected.

3.8 *Hypotheses and Definition of Primary and Secondary Outcomes*

Primary endpoint:
The primary endpoint of the OVIVA study is definite failure of infection treatment identified within 12 months from randomisation, whereby definite failure is indicated by one or more of the following:
a) isolating bacteria from 2 or more samples of bone/spine/peri-prosthetic tissue, where the bacteria are similarly typed
b) a pathogenic organism (e.g. *Staphylococcus aureus* but not *Staphylococcus epidermidis*) on a single, closed, biopsy of native bone or spine
c) diagnostic histology on bone/peri-prosthetic tissue
d) formation of a draining sinus tract arising from bone/prosthesis or
e) recurrence of frank pus adjacent to bone/ prosthesis.

* “similarly typed” refers to the results of routine laboratory work, including bacterial genus/species and the results of routine antibiotic susceptibility testing. We will not require any additional bacterial typing in the laboratory beyond local routine practice.

H_o: The proportion of participants with a definitive treatment failure in the PO group is more than 7.5% higher than the proportion of participants with definitive treatment failure in the IV group:
$p_{PO} - p_{IV} > 7.5\%$, where p_{PO} and p_{IV} are the proportions of participants with definitive treatment failures randomised to the PO and IV strategies respectively
H_1: The proportion of participants with a definitive treatment failure in the PO group is not more than 7.5% higher than the proportion of participants with definitive treatment failure in the IV group:
$p_{PO} - p_{IV} <= 7.5\%$, where p_{PO} and p_{IV} are the proportions of participants with definitive treatment failures randomised to the PO and IV strategies respectively

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Secondary endpoints:

All statistical tests for the secondary endpoints are standard two-sided superiority tests with the exception of 4) below, which is analysed using a non-inferiority approach in line with the primary endpoint.

1) SAEs, including death (i.e. all cause) according to treatment allocation.
   H_o: There is no difference in the odds of experiencing at least one SAE in both randomised trial arms:
   $OR_{PO/IV} = 1$, where $OR_{PO/IV}$ = odds of experiencing an SAE in the PO arm / odds of experiencing an SAE in the IV arm
   H_1: There is a difference in the odds of experiencing at least one SAE between the randomised trial arms:
   $OR_{PO/IV} \neq 1$, where $OR_{PO/IV}$ = odds of experiencing an SAE in the PO arm / odds of experiencing an SAE in the IV arm
2) The frequency of line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line).
   As this summary includes primarily participants randomised to the IV strategy, no formal statistical tests will be performed.
3) The proportion of participants with *Clostridium difficile* associated diarrhoea in each treatment arm.
   H_o: There is no difference in the odds of experiencing at least one with *Clostridium difficile* associated diarrhoea in both randomised trial arms:
   $OR_{PO/IV} = 1$, where $OR_{PO/IV}$ = odds of experiencing *Clostridium difficile* associated diarrhoea in the PO arm / odds of experiencing *Clostridium difficile* associated diarrhoea in the IV arm
   H_1: There is a difference in the odds of experiencing with *Clostridium difficile* associated diarrhoea between the randomised trial arms:
   $OR_{PO/IV} \neq 1$, where $OR_{PO/IV}$ = odds of experiencing with *Clostridium difficile* associated diarrhoea in the PO arm / odds of experiencing with *Clostridium difficile* associated diarrhoea in the IV arm
4) The frequency of the secondary endpoints "probable" or "possible" treatment failure as composites with definitive treatment failure. These will be determined by blinded endpoint committee review, and determined according to the following criteria;
   a) Loosening of a prosthesis, confirmed radiologically OR
   b) non-union of a fracture after 6 months, confirmed radiologically OR
   c) superficial spreading erythema, treated as cellulitis with an antibiotic for >1 week; where results from deep tissue samples do not meet the primary endpoint as described above.
   Where appropriate deep tissue samples are sent for microbiology and results of culture are negative, either of a), b) or c) are met, then the endpoint will be regarded as "possible". On the other hand, where deep tissue samples are not sent for microbiology, and either a), b) or c) are met, then the endpoint will be regarded as "probable".

   H_o: The proportion of participants with any treatment failure in the PO group is more than 7.5% higher than the proportion of participants with any treatment failures in the IV group.
   $p_{PO} - p_{IV} > 7.5\%$, where p_{PO} and p_{IV} are the proportions of participants with any treatment failures randomised to the PO and IV strategies respectively
   H_1: The proportion of participants with any treatment failure in the PO group is not more than 7.5% higher than the proportion of participants with any treatment failure in the IV group.
   $p_{PO} - p_{IV} <= 7.5\%$, where p_{PO} and p_{IV} are the proportions of participants with any treatment failures randomised to the PO and IV strategies respectively
5) Early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason.

H_o: There is no association between early termination of the planned six week strategy and the randomisation allocation.
H_1: There is an association between early termination of the planned six week strategy and the randomisation allocation.

6) Resource allocation determined by; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs.
Refer to the separate health economics analysis plan for the hypotheses for the relevant analyses.
7) Quality of life evaluated by EQ-5D-3L questionnaire
H_o: There is no difference in the median EQ-5D-3L index between the two randomised trial arms
Median (EQ-5D-3L $_{PO}$) = Median (EQ-5D-3L $_{IV}$)
H_1: There is a difference in the median EQ-5D index between the two randomised trial arms
Median (EQ-5D-3L $_{PO}$ ≠ Median (EQ-5D-3L $_{IV}$)
8) Oxford Hip and Knee Scores (where infection is in the hip or knee)
H_o: There is no difference in the median OHS/ OKS between the two randomised trial arms.
Median (OHS_{PO} = Median (OHS_{IV})
Median (OKS_{PO} = Median (OKS_{IV})
H_1: There is a difference in the median OHS/ OKS index between the two randomised trial arms.
Median (OHS_{PO} ≠ Median (OHS_{IV})
Median (OKS_{PO} ≠ Median (OKS_{IV})
9) Adherence to oral medication in terms of the MEMS caps. As this summary includes participants randomised to the PO strategy only, no formal statistical tests will be performed.

Secondary endpoints 1, 2, 4 and 5 will be determined by study clinicians. The primary endpoint and secondary endpoint 4 will be determined by the blinded endpoint committee using redacted notes. Secondary endpoints 6 and 7 will be determined by participants with evidence of infection in the hip and knee respectively using questionnaires. Secondary endpoint 8 will be determined in a subset (i.e. Oxford, Guy's and St Thomas' Trusts, Royal Free Hospital Trust and the Royal National Orthopaedic Hospital) using MEMS.

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3.9 *Outcomes Assessment Schedule*

Baseline assessments are performed prior to randomisation on day 0.
Table 1 below details all important time points and assessments in the study.

Table 1: OVIVA assessment schedule

Time	Activity
Day -7 to 0	Definitive surgical procedure (see above for definition) or, where not applicable, the start of antibiotic treatment for the current clinical episode of illness should be within this period.
Antibiotic prescribing	
Day 0	Randomized to oral vs IV strategy. May continue on intravenous antibiotics within the "oral strategy" up to 7 days in total (including pre-randomization IV antibiotics given for current clinical episode).
Days 0-42	Period during which randomized therapy (i.e. Oral or intravenous antibiotics) is given. MEMS will be provided if applicable (see below)
Day 42 onwards	May receive further oral antibiotics as clinically appropriate. These further antibiotics are not determined by randomization.
Clinic Reviews	
Day 42 (accepted range 21 to 63)	Investigator completes 1st review. Collects MEMS if used.
Day 120 (accepted range 70 to 180)	Investigator completes 2nd review. Collects MEMS if used and not previously collected.
Day 365 (accepted range 250 to 420)	Investigator completes 3rd review and end of study follow up.
Questionnaires	
Day 0, 14, 42, 120, 365 and at endpoint or SAE	EQ-5D-3L questionnaire
Day 0, 120, 365	Oxford Hip/Knee Questionnaire

3.10 *Data Management Responsibility*

Monitoring involves overseeing the progress of the trial by confirming the data is accurate, complete and verifiable from source documents. Using the OVIVA Monitoring Plan V1, Sept 2014, we are conducting monitoring visits to our collaborating sites, which involves confirmation of correct consenting and storage, reviewing of eligibility before randomisation, primary outcome data, CRF validation, questionnaire data accuracy against source data, and safe storage of all data and documentation. Using the OpenClinica Database, the study co-ordinator regularly reviews any missing data, and sends sites data missing reports using the OVIVA Data Queries/Monitoring Form V1, Sept.2014 (adapted from OCTRU-OF-015_V1.0).

4. Quality Control and Data Validation

Throughout the trial, data checks will be performed in conjunction with data collection and data entry.
Prior to any analysis, the Trial Statistician will perform additional data checks and validations, investigating the data for outliers and inconsistent dates. All apparent outliers will be checked against paper records and either confirmed as valid observations or corrected.
For the final analysis a manual 100% data entry check of the results of the reviews performed by the Endpoint Review Committee against the information on treatment failures as read into Stata will be performed. The results from the review are usually received in table format (e.g. Microsoft Excel). This review will include all participants for whom potential treatment failures have been recorded and whose redacted notes have therefore been reviewed by the Endpoint Review Committee.
Data entry for PROMS (i.e. the EQ-5D-3L, the compliance questionnaire for PO patients and the OKS/OHS where appropriate), as well as baseline infection categories as defined by the endpoint review committee (for non-definite infections) will be checked against the paper CRFs for 20 patients. Additional data checks are performed if the error rate is found to be greater than 1%. Using the OVIVA Study Monitoring Plan (V1, Sept 2014), we have commenced checking the baseline infection rates, and all questionnaire data against source data in the clinical notes and from microbiology results, and from source questionnaires for 10% of the total study participants, for two collaborator sites, so far. We intend to continue with more monitoring visits over the next few months. The OpenClinica database is regularly checked and queries are raised with collaborating sites for possible inconsistencies and missing data (see 3.2)

The analysis for the primary endpoint will be repeated by a second statistician. The performance of a second analysis for the primary endpoint will be reported in the final statistical report. Information on randomisation allocation and endpoints will be cleaned and transferred securely to the second statistician, who will independently perform the primary outcome analysis in Stata, or another validated statistical package.

The statistical report will be reviewed by a second statistician to ensure that the SAP/principles of the SAP have been followed as per the OCTRU SOP STATS-005.

5. Data SAFETY monitoring Committee and Interim Analyses

A data safety monitoring board will be formed, which is independent from the study team and the sponsor. The DMC will be composed of 3 members; Neil French (chair, Professor of Infectious Disease, Liverpool University), Colette Smith (Lecturer in Biostatistics, UCL) and Martin Llewelyn (Reader in Infectious Diseases and Therapeutics, Brighton and Sussex University). If, during the course of the trial, one of the DMC members withdraws, a replacement with a similar background will be identified.

The DMC will meet (either in person or by teleconference) to discuss the study design and SOPs shortly before the start of the study. Investigators will participate in this meeting. The DMC will also evaluate the frequency of endpoints in an unblinded analysis, when investigators will not be present. The DMC will make a recommendation before investigators proceed with the multi-centre trial.
A full interim analysis including all available data from all sites will be reviewed by the DMC after approximately 100 participants from sites other than Oxford have been recruited and completed their follow-up to review the safety and ethics of the OVIVA trial.
Extra meetings may be convened at the request of the investigators, sponsor, or DMC members to discuss emerging data that is a cause for concern.

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It is expected that the DMC would only recommend early stopping if there was a very significantly worse outcome in the PO antibiotic group compared to the IV group (i.e. using the Haybittle-Peto stopping boundary).
The DMC will discuss the analysis plan before the investigators conduct the final analysis

6. Descriptive Analyses

6.1 *Representativeness of Study Sample and Patient Throughput*

A complete CONSORT flow diagram will be included in the trial report, clearly stating the number of patients screened, eligible, randomised and followed-up throughout the trial. Information on reasons for ineligibility will be given; information on randomisations and follow-up will be presented by treatment arm and detail how many participants received their allocated intervention.

6.2 *Baseline Comparability of Randomised Groups*

For all information collected at baseline, numbers (with percentages) for binary and categorical variables (including gender) and means (with standard deviations), or medians (with the interquartile range and range) for continuous variables (including baseline patient reported outcomes and age) will be presented overall and by treatment group.
There will be no tests of statistical significance or confidence intervals for differences between randomised groups on any baseline variable because, by definition of randomisation, these arise only due to chance.

6.3 *Comparison of Losses to Follow-up*

The numbers (with percentages) of losses to follow-up (defaulters and withdrawals) over the one year period of the study will be reported and compared between the PO and IV groups using frequency and percentages. Any deaths (and their causes) will be reported separately within the section on SAEs and complications.

6.4 *Description of Available Data*

The availability of data for baseline assessments as well as for primary and secondary endpoints will be described for all appropriate trial time points.
Data items are defined as available if either the clinic assessment form has been completed, or for patient reported outcome measures, if the information provided can be used in the analysis. For example, the OKS/ OHS final scores can only be calculated when no more than two items are missing. Hence the OKS/ OHS will be classed as available if the responses to at least 10 of the 12 items are available.

Summaries will be provided overall and by trial arm, and the number of available data items will be presented together with the number of data item expected and a percentage indicating the rate of data compliance for each endpoint and time point (i.e. investigating what percentage of expected data is actually available).

6.5 *Description of Compliance with Intervention*

Early termination of the planned six week period of oral or IV antibiotics, as well as adherence to the medication are secondary endpoints of the OVIVA trial and will be summarised in the endpoint relevant section.

6.6 *Unblinding of Randomised Treatments*

N/A – OVIVA is an open label trial and participants and staff are not blinded to treatment allocations, but the independent Endpoint Review Committee is blinded to participants' treatment allocations.

6.7 *Reliability*

The trial is open-label, as blinding is not possible, since giving a prolonged intravenous placebo treatment was considered unethical. Open label studies are at risk of bias. Objective criteria for meeting the primary endpoint were therefore set out, which will be examined by a blinded endpoint review committee.

For any participant that is admitted to hospital with signs or symptoms relating to the original site of infection, investigators will send a redacted copy of the inpatient admission notes to the endpoint review committee. Notes will be redacted for personal identifiable information and for antibiotic names or routes of administration. One member of the committee will be expected to review the notes in detail, and summarise the key findings that determine an endpoint for the other committee members. Blind to the treatment allocation, the committee will determine an endpoint either by consensus following discussion, or by a vote called by the chair if consensus cannot be reached.
The endpoint committee will meet at regular intervals throughout the recruitment and follow-up of the trial, to ensure that up-to-date information on endpoints is available for interim DMC meetings.

With regards to the trial outcomes, the endpoint committee will only be required to review potential treatment failure. All other secondary endpoints including SAEs, line complications, early termination of treatment patient reported outcome data and data for resource allocation will be determined directly by the local study clinicians, or completed by the trial participants.

The endpoint committee will also have a role in determining diagnostic sub-groups for the infection criteria at baseline, following the guidance listed below:

"Definitive" evidence of infection, defined by one or more of the following:

a) isolating bacteria from 2 or more samples of bone/spine/peri-prosthetic tissue, where the bacteria are similarly typed
b) a pathogenic organism (e.g. *Staphylococcus aureus* but not *Staphylococcus epidermidis*) on a single, closed, biopsy of native bone or spine
c) diagnostic histology on bone/peri-prosthetic tissue
d) a draining sinus tract arising from bone/prosthesis or
e) frank pus adjacent to bone/ prosthesis.

If any of these criteria are met, then the category "definitive" infection will be applied without endpoint committee review.
Where these criteria are not met, the endpoint committee will be sent a redacted copy of the patient's admission notes and laboratory results from the time of randomisation, and apply the following criteria to determine "probable" or "possible" infection:

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Infection will be categorized as "probable" where microbiological sampling has not been undertaken, AND none of the other criteria for definite infection are fulfilled AND any one of the following are met:

a) Radiological or operative findings of periosteal changes suggesting chronic osteomyelitis OR
b) Radiological findings suggesting discitis/spinal infection OR
c) The development of a discharging wound after an orthopaedic procedure where prosthetic material has been implanted OR
d) The presence of deep pus close to but not adjacent to bone/prosthetic joint/orthopaedic device OR
e) The presence of peri-prosthetic necrotic bone OR
f) Rapid loosening of a joint prosthesis/orthopaedic device (i.e. leading to localized pain in less than 3 months since implantation) in the absence of a mechanical explanation for rapid loosening.

Infection will be categorized as "possible" where microbiological sampling has been undertaken with negative results (according to criteria described above for "definite" infection) AND other criteria for definite infection are not fulfilled AND in addition one or more of the criteria listed a) to e) above is met.

A sample of all derived and generated variables to be used for the trial analysis will be verified, in accordance with the OCTRU SOP STATS-003.

7. Patient Groups for Analysis

The following patient populations will be utilised in the analyses:

Intent to treat (ITT): All randomised participants will be analysed according to their allocated intervention.

Modified intention to treat analysis (MITT): Randomisation participants will be analysed according to their allocated intervention if they have non-missing outcome data. For adjusted analyses, relevant baseline variables that are used to adjust the model also need to be available in order for participants to be included in the MITT population.

Per protocol (PP): All participants who have received at least four weeks of their randomised strategy, and, if in the PO group, did not exceed the limits set for the use of IV antibiotics (i.e. 5 days continuously at any one time). Participants who were recorded to have exited early from their randomised strategy due to possible or probable recurrence of infection will also be included in the PP population. Participants will be included in the PP analyses if sufficient outcome and baseline data (where relevant) is available.

8. Analyses to address primary aims

It is anticipated that the analysis will use STATA statistical software, or other validated statistical software, such as SAS or R (versions will be recorded in the Statistical report).

8.1 *Evaluation/Definition of Primary Outcome (where applicable)*

The primary endpoint of the OVIVA trial, i.e. definite failure of infection treatment, as defined in section 3.8, is reached if any of the reports of potential treatment failures as recorded by the local

clinical team are confirmed as a definite failure of infection treatment by the endpoint review committee. This endpoint will be analysed primarily as a binary outcome (i.e. not as a time to event outcome) because dates may reflect timing of observations rather than actual failure.

8.2 *Statistical Methods Used for Analysis of Primary Outcome*

Primary analysis

Based on the intention to treat population, the proportions of participants experiencing the primary endpoint (i.e. definitive treatment failure as adjudicated by a blinded endpoint review committee) will be tabulated by treatment group (i.e. oral vs intravenous therapy). If the absolute, upper two-sided 90% confidence interval (CI) around the absolute unadjusted difference (i.e. oral-intravenous) is less than 7.5%, then the criteria of non-inferiority will be met.

The primary analysis is an unadjusted analysis. Therefore, a complete cases analysis, whereby participants with missing outcome data are excluded, makes the assumption that the data is missing completely at random. This is, the probability of data being missing does not depend on observed or unobserved measurements. This is a very strong assumption, which is unlikely to hold in practice.

Therefore, the ITT population forms the basis of the primary analysis. This includes all randomised participants within their randomised treatment allocations regardless of their compliance with the protocol. Participants with missing outcome data are not excluded from this analysis. Therefore assumptions have to be made about their outcomes.

The originally specified analysis classed individuals with incomplete follow-up and no event observed to date as not having experienced an endpoint. This is essentially a single “hard” imputation of no event for these participants. This analysis will now be performed as a supporting analysis, and multiple imputation (MI) will form the basis of the primary analysis.

Under MI, data are assumed to be missing at random, i.e. missing data are dependent on the values of observed data, but are independent of the values of the missing data themselves once observed data have been accounted for. This assumption is more likely to hold in practice than the missing completely at random assumption, and its robustness can be assessed in appropriate sensitivity analyses.

MI imputes missing data based on information from other observed variables. Several imputations are generated and combined under Rubin’s Rule to account for the uncertainty around the imputed values(2). Missing values for the primary outcome will be imputed based on a logistic regression model, such as the *mi impute* command in Stata.

Hence, the primary analysis of the OVIVA trial is based on the ITT population whereby missing data is handled using an MI approach.

The following variables are used in the imputation model, and were identified as relevant in predicting outcomes by the OVIVA CI:

- infection details at baseline are combined as follows and used as binary variables in the imputation model:
  - Chronic osteomyelitis debrided, no current implant or device OR discitis/ spinal osteomyelitis/ epidural abscess debrided
  - Chronic osteomyelitis as above, but not debrided OR discitis/ spinal osteomyelitis/ epidural abscess but not debrided
  - Implant or device present and retained (“DAIR”)
  - Removal of orthopaedic device for infection OR prosthetic joint implant removed
  - Prosthetic joint implant, 1-stage revision
- Whether or not antibiotic beads/ cement were used in the index operation
- Participants’ comorbidity status (yes vs. no):
  - Diabetes

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    - Peripheral vascular disease in participants with foot infections
    - Current smoker
    - Rheumatoid arthritis or systemic autoimmune disease
- Staph Aureus present in samples taken before randomisation
- Pseudomonas sp present in samples taken before randomisation
- Age
- Gender

Due to the large number of binary variables used in the MICE model, resulting in a high likelihood of perfect predictions, convergence issues of the imputation model are anticipated. This will be addressed by augmenting the data, i.e. adding a small number of additional observations with small weights when model parameters are estimated to prevent perfect prediction(3, 4).
Non-linearity in the relationship between age and outcome will be explored in the complete cases. If there is clear evidence of non-linearity, the multiple imputation model will be adjusted appropriately (for example, age may be modelled using natural cubic splines).

Supporting analyses

A number of supporting analyses will be performed. These will focus on the consistency of the point estimates and two-sided 90% CIs rather than formal comparison with the 7.5% non-inferiority margin. Details of these analyses are given below, or in the section on subgroup analyses:

Initial supporting analyses will include the following deviations from the above described primary analysis, using different analysis populations and assumptions about missing data about:

- The MITT population will be used, i.e. the analysis will be performed on the complete cases only, without imputation of missing outcomes. Participants are analysed based on their randomisation allocation.
- The ITT population will be used; however, in this analysis, all participants with incomplete follow-up and no event observed to date will be classed as not having experienced an endpoint (single imputation). Death without clinical failure is not classed as a treatment failure for this analysis. This analysis was initially defined as the primary trial analysis, but was moved to the supporting analyses in favour of a multiple imputation approach for handling missing data. Participants are analysed based on their randomisation allocation.
- The PP population will be used. Participants are analysed based on their randomisation allocation, but are excluded from the analysis if they do not meet the PP population criteria.

In addition, a logistic regression model will be used to calculate the estimates of the treatment differences for the occurrence of definite treatment failure as adjudicated by the blinded endpoint review committee adjusted for age, comorbidity, infecting pathogen, and type of infection.
Additional information on the categorisation of the infecting pathogen and type of infection can be found in sections 0 and 0 respectively. Categories with low counts may be combined.
Information on 11 comorbidities is collected at enrolment, and these comorbidities will be added to the model as separate binary variables. In the event of comorbidities with very low counts, these comorbidities may be combined to avoid difficulties with the maximum likelihood estimation of the logistic model. Where no information has been entered on the comorbidities, the participants will be considered not to suffer from these comorbidities. The imputed endpoints and explanatory variables from the primary analysis will be used; however, participants with missing data for the infecting pathogen will be excluded from this analysis.

For the multivariate logistic regression models, residual and predicted values produced form the model will be examined to assess the assumptions of the model. Specifically, the assumption of linearity between the predicted log odds and the covariates is assessed by plotting lowess graphs. The independence of the error terms will be considered. Influential cases are investigated by plotting the standardised Pearson's residuals against the predicted probabilities and the leverage of the individual observations.

To assess any potential bias in the post-randomisation surveillance, which would present as a delay in time to meeting a definitive endpoint in one randomised group, as well as loss to follow-up or death without and event, a time to event analysis will be performed.
The Cox proportional hazards model (if appropriate) will be used to compare the time to first treatment failure between the trial arms. The model will not be adjusted for baseline characteristics, as this analysis is focussing on the timing of events. Participants with no treatment failures will be censored at the earliest of the following dates: death, last assessment if they are not known to have died and were lost to follow-up prior to their one year assessment, or at the date of their one year follow-up. Treatment estimates, standard errors, hazard ratios and 95% confidence intervals, as well as p-values will be presented. Failure free time to event curves will be calculated using the Kaplan-Meier curves will be presented for the time to meeting an endpoint by trial arm. This analysis will be performed for the ITT population only.

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The proportional hazards assumption will be assessed by plotting the hazards over time (i.e. the log cumulative hazard plot) for both treatment arms, investigating the log-log plots of the hazards and a test for proportionality. Should these assessments indicate non-proportional hazard rates, alternative approaches will be examined, e.g. piecewise hazards.

8.3 *Adjustment of P values for Multiple Testing*

There is no multiple testing as only a single primary outcome is considered. All additional analyses are undertaken with an intention to further inform the results from the primary analysis. Therefore significance levels used will be 0.05 and 95% confidence intervals will be reported.

The DMC will review interim summaries and a formal interim analysis. However it is expected that the DMC would only recommend early stopping if there was a very significantly worse outcome in the PO antibiotic group compared to the IV group (i.e. using the Haybittle-Peto stopping boundary). Therefore, the significance level used to determine early termination of the trial is very low (i.e. 0.001) and no formal adjustment of the p-value for the final analysis is considered necessary.

8.4 *Missing Data*

The primary outcome of the OVIVA trial, i.e. definitive treatment failure as adjudicated by a blinded endpoint review committee does not rely on trial specific clinic assessments or patients reports, but can be obtained from hospital notes. Therefore, only minimal amounts of missing data are expected, primarily in cases where participants formally withdraw from all further follow-up or relocate or their medical records can no longer be accessed.

In the primary analysis, multiple imputation is utilised. Additional complete cases analyses are also performed. These analysis make strong assumptions about the underlying missing data mechanism, assuming that data is either missing at random or missing completely at random.

Sensitivity analyses will assess the robustness of these analyses, by also considering the impact on the study results if data are assumed to be missing not at random, i.e. if those with missing data have better or worse outcomes than those with completely observed outcome data. The sensitivity analysis will include a tipping point analysis(5-7), whereby the departures from the missing completely at random assumption needed to change the trial results will be explored. In discussion with the CI and clinical team, the robustness of the trial results with regards to missing data will be discussed.

8.5 *Pre-specified Subgroup Analysis*

All subgroup analyses will be based on the MITT population (complete cases analysis) and presented as forest plots.

8.5.1 Pre- specified Subgroup Analysis considering infection subgroups at randomisation

Taking into account the subgroups of participants with firstly a “definite” infection (vs. “probably”/ “possible” infection) at randomisation, and secondly the participants with a “definite” or “probable” infection (vs. “possible” infection) at randomisation. For the ITT population, a logistic regression model will be constructed with the occurrence of the primary endpoints (i.e. definite treatment failure as adjudicated by the blinded endpoint review committee) as the outcome, and the randomised treatment as well as the subgroups of infection at randomisation (“definite” vs. “probable”/ “possible” infection in the first statistical model, and “definite”/ “probable” vs.

"possible" infection in the second statistical model) as explanatory variables, as well as the interactions between the randomised treatment and the infection subgroup at randomisation.

Note: There are some participants for whom the infection subgroup at baseline could not be confirmed by the review committee. A decision was made by the trial team to include these participants into the "possible infection" category. This is because they were felt to have clinical evidence of infection at randomisation.

8.5.2 Pre-specified Subgroup Analysis considering the type of infection

Sub-group analysis will be used to determine the consistency of treatment effects by type of infection.

Information on the type of infection is collected at the enrolment of trial participants, and categorised as follows:

1. Chronic osteomyelitis debrided, no current implant or device OR
   Discitis/spinal osteomyelitis/ epidural abscess debrided
2. Chronic osteomyelitis as above, but not debrided OR
   Discitis/spinal osteomyelitis/ epidural abscess but not debrided
3. Implant or device present and retained (i.e. "DAIR")
4. Removal of orthopaedic device for infection OR
   Prosthetic joint implant removed
5. Prosthetic joint implant, 1-stage revision
6. OVIVA infection criteria not met

Where participants fall into more than one category, they will be assigned to the highest numeric category in the above list. Categories with very low counts may be combined with the next (lower) category.

For the ITT population, a logistic regression model will be constructed with the occurrence of the primary endpoint (i.e. definite treatment failure as adjudicated by the blinded endpoint review committee) as the outcome, and the randomised treatment as well as the infection type (as a 6 level categorical variable) and the interaction between randomised treatment and infection type as explanatory variables. The test for heterogeneity is the 5df test that the effect of randomised treatment is the same across all levels of infection type, i.e. that each interaction coefficient is zero.

8.5.3 Pre-specified Subgroup Analysis considering the infecting pathogen

Sub-group analysis will be used to determine the consistency of treatment effects by infecting pathogen.

Information on the following five infecting pathogens is collected:

1. Staph Aureus
2. Pseudomonas spp
3. Gram negative organism(s)
4. Streptococcus
5. Coagulase negative Staphylococcus
6. No infecting pathogen present

Where evidence for more than one of the above pathogens is present on the deep tissue microbiology results taken prior to randomisation, they will be assigned to the highest numeric category in the above list. The infecting pathogen will be a single variable with six levels.

The above categories for the infecting pathogens have been chosen as part of a pragmatic approach and include the main gram positive categories. It was felt that insufficient numbers of patients would be available for other infecting pathogens to enable meaningful statistical subgroup analysis.

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For the ITT population, a logistic regression model will be constructed with the occurrence of the primary endpoints (i.e. definite treatment failure as adjudicated by the blinded endpoint review committee) as the outcome, and the randomised treatment as well as the infecting pathogen and the interaction between randomised treatment and infecting pathogen.

8.5.4 Pre-specified Subgroup Analysis considering the intended and actual antibiotic choice

In some centres, randomisation to oral antibiotics may result in an increased use of antibiotics with particular properties in penetrating biofilms, such as rifampicin. Subgroup analysis will be used to assess the effect of potentially different treatment choices between the trial arms.

Both intended IV and oral antibiotic choices pre-randomisation, and actual antibiotic choices post-randomisation to either oral or IV, were collected. Actual antibiotic choices are a post-randomisation variable and therefore it is not possible to exclude some influence of randomisation on these choices. This will be assessed by comparing intended vs. actual antibiotics for the group the patient was actually randomised to.

As there is particular interest in rifampicin, a specific subgroup analysis will be conducted for this variable. A variable will be created indicating whether or not rifampicin was an antibiotic choice for the intravenous and oral arm, using the treatment intentions for both treatments as recorded prior to randomisation.

Using the the ITT population, a logistic regression model will be constructed with the occurrence of the primary endpoints (i.e. definite treatment failure as adjudicated by the blinded endpoint review committee) as the outcome, and the randomised treatment as well as the above described indicator variable (rifampicin was an intended treatment option yes vs. no) and the interaction between the two variables.

An additional subgroup analysis will consider the clinician's specific antibiotic intentions recorded prior to randomisation, as a categorical variable. The antibiotic intentions will be categorised into the following groups based on the intended drug. Where multiple antibiotics were taken, patients will be assigned to the highest numeric category in the below list.

Planned IV treatments	**Planned PO treatments**
1. Glycopeptides (i.e. teicoplanin / vancomycin)	1. Penicillins
2. Penicillins	2.Quinolones
3. Cephalosporins	3. Tetracyclines
4. Carbapenems	4. Macrolides / Lincosamide
5. Other single IV antibiotic	5. Other single PO antibiotic
6. Combination IV antibiotics	6. Combination PO antibiotics

For the ITT population, a logistic regression model will be constructed with the occurrence of the primary endpoints (i.e. definite treatment failure as adjudicated by the blinded endpoint review committee) as the outcome, and the randomised treatment as well as the subcategory of the antibiotic intention and the interaction between the two variables.

For all pre-specified subgroup analyses, diagnostic checks will be performed as described in section 8.2.

8.6 *Treatment by Centre Interaction*

Consistency of potential effects will be assessed across all centres by informal examination of the within centre effects. There will be limited capacity to investigate these formally and it is noted that such centre effects are expected by chance.

Treatment allocation by centre interaction will be explored and odds ratios will be presented as forest plots without the performance of statistical tests.

This summary will only include centres where patients in both arms have experience treatment failures, as the odds ratios can otherwise not be estimated.

8.7 *Sensitivity Analysis*

No sensitivity analysis in addition to that discussed in the above sections is planned in the context of the primary analysis. The trial team feels that the above described analyses (including the PP analysis, which is part of the primary analysis described above, and sensitivity analysis to explore the potential effects of missing data) are sufficient to assess the robustness of the trial results.

9. Analysis to address secondary aims

The secondary aims of the study are to determine the effect of oral versus intravenous antibiotic strategies on SAEs, the frequency of line complications, “possible” and “probable” treatment failures as composites with “definite” treatment failures, early termination of the planned six week treatment period, quality of life measured by the EQ-5D-3L for all participants and the OKS/ OHS in the relevant subset of participants, adherence to the allocated intervention and cost-effectiveness. These analyses are performed on the MITT population.

More details on the secondary endpoints are provided in section 141.

9.1 *Evaluation/Definition of Secondary Outcomes (where applicable)*

- The “probable” and “possible”, as well as “definite” treatment failures are determined by the blinded endpoint review committee and are not derived as part of this analysis.
- Early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason is defined as exiting the allocated strategy
- The patient reported outcomes (EQ-5D-3L, OKS and OHS).

  For MEMS, adherence will be calculated by the supplies, medAmigo, as follows: During the period of monitoring, a day-by-day proportion of correct dosing is calculated by dividing the number of MEMS openings by the number of dose prescribed that day. When there are more MEMS openings than dose prescribed that day, these extra openings (can be driven by extra intakes or artificial openings for a refill/data download) are not taken into account in the calculation. This implies that the calculation is capped by 100% or overdose is not taken into account.

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9.2 *Statistical Methods Used for Analysis of Secondary Outcomes*

9.2.1 "possible" and "probable" treatment failures as composites with "definite" treatment failures

A breakdown of the types of treatment failures recorded by trial arm will be provided, together with a summary of the number and type of treatment failures experience within each arm.
The primary analysis described in section 8.2 will be repeated for occurrence of the composite of "possible", "probable" and "definite" treatment failures. Secondary analyses described in section 8.2 will not be performed. Subgroup analyses described in section 8.5 will be performed for the MITT population only.

9.2.2 Adverse events and complications

Episodes of *Clostridium difficile* will be summarised overall and by treatment arm (frequency and percentages). Participants will be categorised as either having or not having experienced episodes of *C. difficile*. Using this as a binary outcome variable, the unadjusted risk differences in episodes of Clostridium difficile between the treatment arms will be reported for the MITT population.

Reported serious adverse events will also be presented in this section. This includes the number of participants with at least one recorded severe adverse event, as well as the number of severe adverse events reported per participant. In addition, summaries will include the timing of the report from randomisation and whether complications were expected and/ or thought to be related to the randomisation, and the outcome of any SAEs will be summarised. Full details will be given for SAE that are related to the randomisation.

A Chi-squared test will be used to assess if there is evidence of an association between the allocated treatment and the occurrence of at least one SAE for participants (using a binary indicator variable).

9.2.3 The frequency of line complications

Details of the IV lines used in each arm of the trials will be summarised, detailing the frequency of percentage of PIC, Hickman and other lines used.
The number of participants with line complications on each arm, together with details of the first line complications (infection, thrombosis or other events requiring the removal or replacement of the line) will be presented using frequencies and percentages. Information on removal of the lines as a result of the complications and the replacement of removed lines will also be provided.
These summaries will contain primarily participants randomised to the IV strategy; therefore, no statistical tests will be performed.

9.2.4 Early termination of the planned six week strategy

The frequency and percentage of participants who exited early from their allocated six week strategy for good clinical response vs other reasons (as reported on their day 42 or day 120 CRF) vs completing as planned will be presented by treatment arm and compared using chi-squared tests. If the chi-squared test indicates a difference between arms, multinomial regression will be used to estimate treatment effects of early termination for good clinical response separately from other reasons (vs completion as planned) if sufficient numbers of participants fall into this category to justify the use of a regression model.

9.2.5 Quality of life evaluated by the EQ-5D-3L questionnaire

Frequency and percentages of the number of patients within each level of the five EQ-5D-3L domains will be displayed overall and by treatment arm at baseline, 14, 42, 120 and 365 days. Descriptive statistics of the EQ-5D-3L index scores and EQ-5D-3L VAS will be presented overall and by trial arm and baseline and the relevant follow-up time points. This information will also be displayed using boxplots.

The EQ-5D-3L index score and VAS will be analysed using a quantile regression model adjusted for age, comorbidities, infecting pathogen and type of infection, as defined above. The data will be analysed separately for each follow-up time point.
As discussed in section 8.2, explanatory variables with low counts (comorbidities) and categories with low counts within explanatory variables may be combined.

9.2.6 Quality of life evaluated by the OHS and OKS (where the infection is in the hip and knee respectively)

For patients with an infection in the hip or knee, descriptive statistics will be summarised separately for the OHS and OKS overall and by treatment arm at baseline, 120 and 365 days. The data will also be displayed using boxplots.

The OHS and OKS will be analysed using separate quantile regression models adjusted for the baseline scores, age, comorbidities, infecting pathogen and type of infection, as defined above. The data will be analysed separately for each follow-up time point.
As discussed in section 8.2, explanatory variables with low counts (comorbidities) and categories with low counts within explanatory variables may be combined.

9.2.7 Adherence to oral medication

In a subset of sites (Oxford, Guys and St Thomas' Hospital Trust and Royal Free Hospital Trust) will dispense oral antibiotics in pill containers with a Medication Even Monitoring System (MEMS), whereby sensors in the pill bottle tops can detect opening and closing, and report these events with a date stamp. Results from this recording will be summarised to obtain an additional summary of adherence with the medication schedule.
Particular attention will be paid to the number of days on which all doses were missed and, within the analysis of the MEMS data, the dosing intervals. These will be analysed descriptively, using medians, interquartile ranges and ranges.

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As most of the adherence data is to be completed by PO participants only, no statistical tests will be performed for these summaries.

9.2.8 Agreement between intended and received antibiotics

Agreement between the planned PO and IV antibiotics as stated prior to randomisation and actual antibiotics received will be summarised overall and by treatment arm. The frequency and percentage of participants who received and did not receive their intended treatment as their initial antibiotic regimen will be presented.

Agreement between intended and received antibiotics are categorised as follows:

Full match - received their randomised strategy and remained within the intended antibiotic group

Partial match - received their randomised strategy but deviated from the intended antibiotic group

No Match =early exit from randomised strategy

9.2.9 Antibacterial agents used for treatment

Actual initial antibiotic regimens will be summarised overall and by treatment arm. Each regimen will be classified according to the table in section 8.5.4 and summarised overall and by treatment arm.

Interruptions and changes to initial antibiotic regimen will also be tabulated overall and by treatment arm.

The number of patients continuing long-term antibiotic treatment (after 6 weekswill also be summarised overall and by treatment arm using frequencies and percentages.

Time to permanent discontinuation of all antibiotic treatment (defined as the first day where antibiotics are not taken for the next 14 days) will be compared by treatment arm using Kaplan-Meier curves.

9.2.10 Duration of primary hospital stay

Time from randomisation to discharge, and time from original admission to discharge, will be summarised overall and by treatment group using median (IQR) and compared using ranksum tests.

(Note: re-admission post-discharge is an SAE and would be presented as a secondary endpoint)

9.3 *Resource Use and Cost Data*

A separate analysis plan for the health economics analysis will be written by the trial health economist. Resource use and cost data will only be assessed for the final analysis, but not for the interim analysis.

10. Additional Analyses

10.1 *Exploratory analyses*

If the trial results do not demonstrate non-inferiority of PO, additional analyses will explore differences in the primary outcome for different levels of adherence to the oral antibiotics.

No other additional exploratory analyses are currently planned. If the trial team, in discussion with the DMC or TSC intends to perform any additional analyses, the statistical analysis plan will be updated accordingly. Any exploratory analysis that has not been pre-specified will be clearly marked as such in the final statistical report.

10.2 *Blinded analysis*

N/A – the trial statistician will not be blinded to treatment allocations while preparing and performing the statistical analysis for this trial.

10.3 *Meta-analyses*

No new meta-analysis using the trial results is planned as part of the final analysis, and the trial team are not aware of any new comparable trials in adults.

11. Safety Analysis

SAEs are collected as part of the secondary endpoints and all relevant analysis is details in section 9.

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12. Appendix:

12.1 *Glossary of abbreviations*

CI	Chief Investigator
DMC	Data Monitoring Committee
ITT	Intention to Treat
IV	Intravenous antibiotics
MI	Multiple imputation
MITT	Modified Intention to treat
PO	Per Oral antibiotics
PP	Per protocol
SAP	Statistical Analysis Plan
TSC	Trial Steering Committee

12.2 *EQ-5D-3L scoring details*

The EQ-5D-3L questionnaire used in this study consists of five questions with three levels each, which are scored 1 to3, with 3 indicating the most severe problems. The five domains can be converted to a summary index using a country specific value set. Many statistical programmes include code to perform these calculations.
More detail on this questionnaire and related information can be found within the relevant scoring manual on the EuroQol Group webpage(8).

12.3 *OHS/ OKS scoring details*

The OKS and OHS consist of 12 questions each. Each item has five levels, which are scored from 0 to 4, with 4 being the best outcome. The overall score is calculated by adding up the scores for all 12 items.
If data is missing for one or two items, these values can be replaced by the mean value of all other responses. The overall score cannot be calculated if more than two items are missing.
The paper by Murray et al (2007)(9) can be referred to for additional detail.

13. Document history

Version number Issue date	Author	Significant changes from previous version
V2.0_03Dec2016	Ines Rombach	Implemented changes in line with the updated sample size calculation, and to reflect the updated non-inferiority margin (increased from 5% to 7.5%) in the primary non-inferiority analysis Updated the primary analysis to use a multiple imputation approach.

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This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

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