Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Li H-K, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med 2019;380:425-36. DOI: 10.1056/NEJMoa1710926

Oral Versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA)

Supplemental material - protocol and statistical analysis plan.

This supplement contains the following items:

1. Original protocol as implemented at the start of recruitment, and the final protocol as used at the end of the trial.
2. Original and final statistical analysis plans

Summary of relevant changes:

Protocol:

1) Version 1.6 (30 Sept 2014) – extension of recruitment period
2) Version 2 (1 May 2015) – adjustment of the non-inferiority margin from 5% to 7.5% for the primary analysis

Statistical analysis plan:

1) Version 2 (3 December 2015) – adjustment of the non-inferiority margin
2) Version 2 (3 December 2015) - amendment of the primary analysis to use a multiple imputation approach for missing data in the intention to treat population

Study Title: Randomized open label study of oral versus intravenous antibiotic treatment for bone and joint infections requiring prolonged antibiotic treatment: Multi-centre study.

Original Protocol

Internal Reference No: NCT00974493

Research Ethics Committee Ref: 13/SC/0016 South Central Oxford REC B

Date and Version No: Version 1.3; 11th January 2013

Chief Investigator:	Matthew Scarborough (Oxford University Hospitals) Matthew.scarborough@ouh.nhs.uk Tel 0787 2436461
Investigators:	Philip Bejon (Oxford University Hospitals) Guy Thwaites (Guys and St Thomas' Hospital London) Hemant Pandit (Oxford University Hospitals) Martin McNally (Nuffield Orthopaedic Centre) David Beard (Oxford University, Trials Unit Director, TSC) Cushla Cooper (Oxford University, Trial manager) Andrew Seaton (Gartnavel General Hospital, site PI) Andy Briggs (Glasgow University, Health economics analysis) Rachel Midgley (Oncology Clinical Trials Office, TSC) Carolyn Hemsley (Guys and St Thomas' Hospitals, site PI) Robert Read (University Hospital Southampton, site PI) Jonathan Sandoe (Leeds Teaching Hospitals Trust, site PI) Jonathon Folb (Royal Liverpool University Hospital, site PI) Claire Mackintosh (NHS Lothian, site co-PI) Becky Sutherland (NHS Lothian, site co-PI) Susan Hopkins (Royal Free Hospital, site PI) Damien Mack (Royal Free Hospital, site PI) Simon Warren (Royal National Orthopaedic Hospital, site PI) Sarah Meisner (Royal United Hospital Bath, site PI) Martin Williams (Bristol Royal Infirmary, site PI) Neil Jenkins (Birmingham Heartlands, site PI) Gavin Barlow (Hull Royal Infirmary, site PI) Ashley Price (Newcastle Hospitals Trust, site PI)

	Uli Schwab (Newcastle Hospitals Trust, site PI) Ila Aggarwal (Tayside University Hospitals Trust, site co-PI) Morgan Evans (Tayside University Hospitals Trust, site co-PI) John Williams (James Cook Hospital, Middlesborough, site PI) Elinor Moore (Cambridge University Hospitals, site PI) Ann Chapman (Royal Hallamshire Hospital, Sheffield, site PI) Benjamin Lipsky (Endpoint committee chair) Deepa Bose (Endpoint committee) Harriet Hughes (Endpoint committee) Sarah Walker (Oxford University Hospitals, Statistician)
Sponsor:	Oxford University Hospitals NHS Trust
Funder:	NIHR HTA programme Biomedical Research Centre (salary support)

Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

Principal Investigator	Investigator Signature	Date
(Print Name)		

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

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AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.3	11.01.13	M Scarborough	University Hospital Southampton added as a site, and the Royal Free and Royal National Orthopaedic Hospitals listed as independent sites (5.3.1) Provision for signed assent in the event that a patient loses capacity during the trial.
2	1.3	11.01.13	M Scarborough	(5.5.2) Provision for potential data transfer outside the EU (5.5.2 and 11.4)
3	1.3	11.01.13	M Scarborough	Inclusion with the PIS, an invitation letter from clinicians responsible for participants
4	1.3	11.01.13	M Scarborough	

1 SYNOPSIS

Study Title	Randomized open label study of oral versus intravenous antibiotic treatment for bone and joint infections requiring prolonged antibiotic treatment: Multi-centre study.
Internal ref. no.	
Clinical Phase	Phase IV
Trial Design	Open label, randomized non-inferiority trial
Trial Participants	Inpatients in the NHS trusts taking part in the study (see list in protocol) who are referred for a prolonged course of antibiotic therapy for bone and joint infections.
Planned Sample Size	1050
Follow-up duration	1 year
Planned Trial Period	3 years
Primary Objective	To determine whether oral antibiotics are non-inferior to intravenous antibiotics for serious bone and joint infection, judged by numbers meeting a primary, objective endpoint for definitive treatment failure during 1 year of follow up.
Secondary Objectives	To determine the percentage of patients completing allocated treatment (i.e. oral or intravenous), cost-effectiveness of treatment, safety judged by incidence of severe adverse events and efficacy judged by the frequency of secondary endpoints for efficacy.
Primary Endpoint	Definite failure of infection treatment, defined by objective criteria (specified in detail in the protocol) and determined by blinded endpoint committee review.
Secondary Endpoints	1. Serious adverse events, including death (all cause) 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 defined in detail in the protocol, and determined by blinded endpoint committee review. These secondary endpoints will be analysed as composites of a) definitive and/or probable; or b) definitive and/or probable and/or possible recurrent infection. 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 assessed using; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs. 7. Quality of life evaluated by EQ-5D questionnaire 8. Oxford Hip and Knee Scores (where infection is in the hip or knee), a Patient Reported Outcome Measure selected by the

	Dept. of Health for evaluating outcome after orthopaedic surgery. 9. Adherence to taking medication.
Investigational Medicinal Products	None. Oral versus intravenous antibiotic prescribing strategy will be determined by randomization, but not individual agents.

2 ABBREVIATIONS

Add or delete as appropriate.

AE	Adverse event
AR	Adverse reaction
BJI	Bone and/or Joint Infection
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IV	Intravenous
IRB	Independent Review Board
MEMS	Medication Event Monitoring System (i.e. sensors to detect pill bottle opening and closing)
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
OCTO	Oncology Clinical Trials Office
OPAT	Outpatient Parenteral Antibiotic Therapy
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator

PIL	Participant/ Patient Information Leaflet
PO	Per Oral
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee
TSG	Oxford University Hospitals Trust / University of Oxford Trials Safety Group

3 BACKGROUND AND RATIONALE

Bone and joint infections are common in the UK. In the NHS, 100,000 primary joint replacements and 20,000 femoral neck and long bone repairs are performed each year. Infection of bone or joint complicates around 2000 (2.0%) of these procedures, resulting in disproportionately increased mortality, disability and suffering. Treating these infections costs the NHS £20,000 to 40,000 per patient. In addition, osteomyelitis complicates 20% of foot ulcers in diabetic patients, with an incidence of 0.2% per year, translating to 5,000 episodes per year within the NHS.

A prolonged course (4-6 weeks) of intravenous antibiotics therapy delivered by the intravenous (IV) route is considered the "gold standard" treatment for bone and joint infections [1-3]. The inconvenience and cost of prolonged intravenous antibiotics can be reduced by outpatient antibiotic therapy (OPAT) programmes, and patients with bone or joint infection make up a large proportion of the patients treated by OPAT programmes [4-9]. Many hospitals in the UK lack such programmes, and the cost and risk to the patient is higher if prolonged IV therapy is delivered as an inpatient [6].

However, the evidence base supporting the need for prolonged intravenous antibiotic therapy is, in fact, limited.

Randomized controlled trials have shown that early switches to oral antibiotics are as effective as continued intravenous antibiotics for 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 randomized controlled trials of oral versus intravenous antibiotics for bone and joint infection. A Cochrane review of 8 small trials was able to include 180 participants in a comparison of intravenous versus oral therapy, and concluded there was no evidence of superiority of either treatment [15]. The largest single trial in this meta-analysis comprised 59 patients, and hence these studies have not led to a widespread change in practice in favour of oral antibiotics.

Trials demonstrate high success rates with oral antibiotics for osteomyelitis [16,17] or following an early switch to oral antibiotics for prosthetic joint infection [18]. Larger observational studies have been conducted, and report high success rates among patients treated for prosthetic joint infection with 2 stage surgical revisions with a shortened course of intravenous antibiotics or with insertion of antibiotic cement spacers [19,20].

However, observational comparisons are problematic because it is impossible to exclude "confounding by indication", whereby only patients with better underlying prognosis are switched to oral antibiotics, and do well because of their underlying prognosis, not the oral antibiotics.

There is in vivo and in vitro evidence that highly bioavailable combinations of oral therapy with fluoroquinolones and rifampicin are particularly active in prosthetic joint associated infection [21] and osteomyelitis [22]. More limited data suggests oral fusidic acid-rifampicin combinations may have similar properties [23].

The risks of IV catheter-related infections, vein thrombosis and adverse reactions to the antibiotic agents are well described [5,24]. Oral antibiotic therapy may reduce risk, be more convenient for the patient and less costly. Against this, oral therapy carries the risks of poor adherence, gastro-intestinal intolerance, poor bioavailability of some agents, and the acquisition of antibiotic resistance (e.g. rifampicin [25] or fusidate [26]).

For the majority of bone and joint infections currently treated by OPAT, an oral antibiotic regimen with high oral bioavailability, good tissue penetration and exhibiting activity against the known or likely pathogens may be effective. This strategy, however, has not yet been compared to intravenous treatment in clinical trials involving patients with the common types of infections for which prolonged intravenous antibiotic therapy is commonly prescribed.

We began a pilot study in June 2010 (Study Title: Randomized open label study of oral versus intravenous antibiotic treatment for bone and joint infections requiring prolonged antibiotic treatment: Preliminary study in a single centre, Ethics Ref: 09/H0604/109, Eudract Number: 2009-015744-42). At the time of writing, 24th September 2012, we have recruited 197 patients, and identified 10 primary endpoints and 20 serious adverse events.

We will include the patients from this pilot study in the analysis of the multi-centre trial, and patients who have not completed follow up at the point of beginning the multi-centre trial will complete their follow up under the multi-centre trial protocol.

3.1 Rationale for study

Among the patient groups eligible for this study, 6 weeks of IV therapy is the current standard of care in the hospital trusts taking part in the study. The objective of the study is to compare the efficacy and safety of intravenous versus oral antibiotic therapy for patients with bone and joint infection.

Antibiotics suitable for IV use are often not suitable for oral use (because they are not absorbed), and oral antibiotics are often not suitable for IV use (because they tend to need more frequent dosing than is logistically desirable with outpatient IV therapy). It is therefore not appropriate simply to randomize the route of administration without this affecting the choice of antibiotic. Furthermore, the choice of antibiotic is subject to patient factors, the organism cultured and the site of infection, and the preferred antibiotic may change during treatment as laboratory results are returned or the patient experiences drug reactions. Hence, it is not feasible to develop a protocol specifying anticipated management decisions to cover all eventualities for either IV or oral antibiotic choice.

In this study, we will therefore randomize participants to an oral or IV "strategy," rather than to specific individual antibiotics. The choice of individual antibiotics within the randomized strategy will be made by a clinician trained in managing infection. He/she will consider their bioavailability, side effect profile, spectrum of activity, and, while waiting for culture results, patient risk factors for resistant organisms.

3.2 Minimising Bias

Blinding is not possible, since we consider giving a prolonged intravenous placebo treatment to be unethical. Open label studies are at risk of bias. We have therefore described objective criteria for meeting the primary endpoint, 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. The endpoint committee will determine the endpoint blind to treatment allocation.

4 OBJECTIVES

4.1 Primary Objective

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.

4.2 Secondary Objectives

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 questionnaire
8) Oxford Hip and Knee Scores (where infection is in the hip or knee)
9) Adherence, as indicated a) by questionnaire and b) by MEMS (see below) in a subset of participants.

5 TRIAL DESIGN

5.1 Summary of Trial Design

The trial will be a randomized controlled open label trial of PO versus IV antibiotics. The choice of antibiotic will be left to the clinician caring for the patient, hence the trial compares strategies of antibiotic prescribing (i.e. PO versus IV) rather than individual drugs or specified combinations of drugs. The antibiotic prescribed will be chosen according to the available clinical and microbiological data, in conjunction with local antibiotic guidelines, and will be altered according to good clinical care as new results and clinical information become available. During the study period, a clinician with specialist training in infection will provide consultation as needed to select antibiotics and advise on management.

Patients with bone and joint infection who are referred for an infectious disease opinion will be considered for eligibility by a study clinician. The study clinician will determine if the patient meets the inclusion and exclusion criteria, and, if the patient is willing, the study clinician or a research nurse will obtain informed consent from the patient. If patients provide informed consent, the study clinician or research nurse will then record the clinical diagnosis and demographic data.

Patients may be recruited based on a clinical diagnosis of infection without microbiological results. Patients become ineligible if they have received more than one week of a planned 6-week intravenous course already. Provided the patient is eligible and gives informed consent, he/she will then be randomized to complete the first 6 weeks of antibiotic therapy with the selected course of either IV or PO antibiotic therapy. The choice of antibiotic within IV or PO groups will be determined by the responsible clinician. After this first 6-week period, further "follow on" oral antibiotic treatment will be allowed in both randomized groups, determined by usual

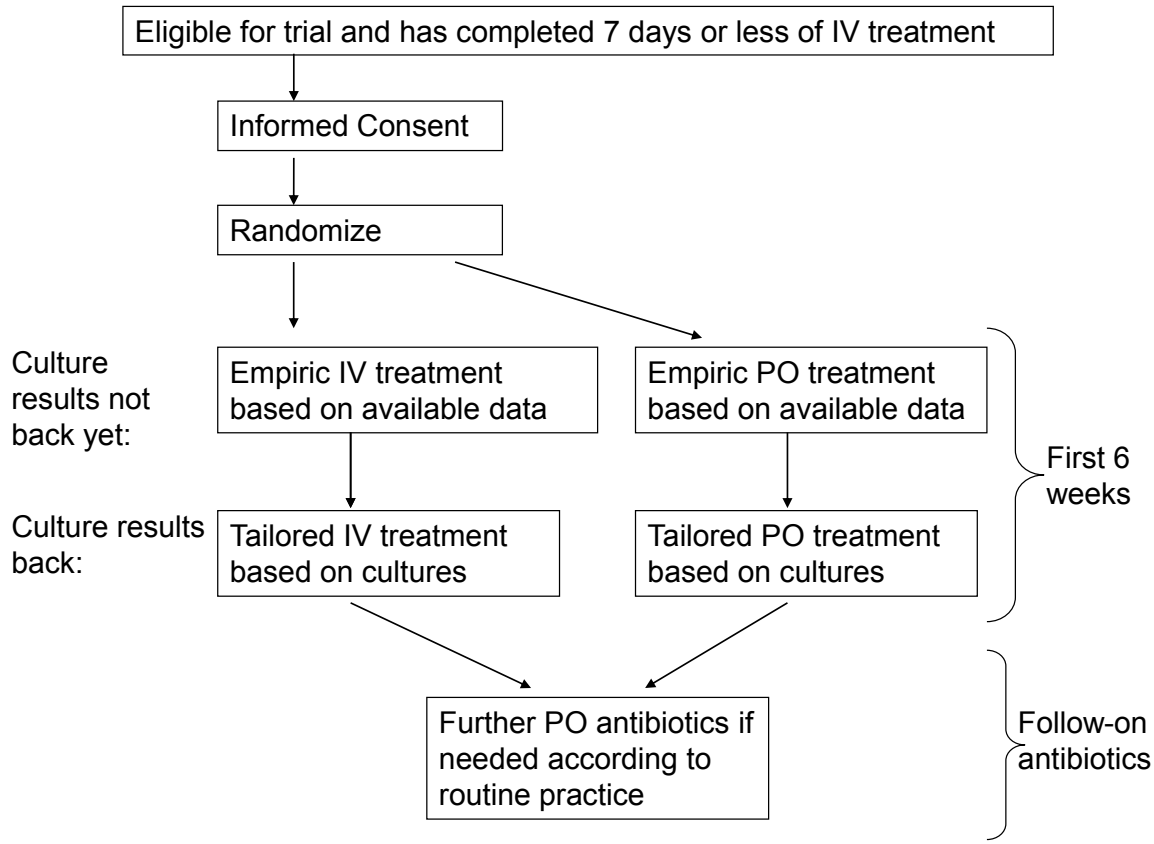
clinical practice. Randomization group will not determine whether "follow on" antibiotics are given, or the length of the "follow on" treatment.

Participants will be seen according to routine policy in the local site, which we anticipate to include visits at least once at ~6 weeks (i.e. day 42, accepted range 21 to 63), once at ~4 months (i.e. day 120, accepted range 70 to 180) and once at ~1 year (i.e. day 365, accepted range 250 to 420) after randomization. Where the patient does not attend for scheduled follow up, the investigator will telephone the participant and/or their GP to identify endpoints that may have occurred at another hospital.

The hospital notes relating to any inpatient admission or outpatient visit where the local clinician identifies a potential treatment failure will be redacted for a) personal identifiable information and b) specifics of antibiotic treatment and/or line insertion.

These redacted notes will be forwarded to the blinded endpoint committee, who will determine whether an endpoint has been met.

Figure 1: Summary of Trial Design



5.2 Primary and Secondary Endpoints/Outcome Measures

Endpoints will be identified by prospective surveillance throughout the year post-randomization.

The trial is open-label. The documentation for all endpoints will therefore be reviewed by an endpoint committee, blind to the treatment group.

5.2.1 Primary

The primary endpoint will be definite failure of infection treatment, where 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 OR

b) a pathogenic organism (e.g. *Staphylococcus aureus* but not *Staphylococcus epidermidis*) on a single, closed, biopsy of native bone or spine OR

c) diagnostic histology on bone/peri-prosthetic tissue OR

d) formation of a draining sinus tract arising from bone/prosthesis or 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.

5.2.2 Secondary

Secondary endpoints will be;

1) SAEs, including death (i.e. all cause) according to treatment allocation.
2) the frequency of line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line).
3) 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".
4) early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason.
5) resource allocation determined by; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs.
6) Quality of life evaluated by EQ-5D questionnaire
7) Oxford Hip and Knee Scores (where infection is in the hip or knee)
8) Adherence to oral medication

Secondary endpoints 1, 2, 4 and 5 will be determined by study clinicians. Primary endpoints and secondary endpoint 3 will be determined by the blinded endpoint committee using redacted notes. Secondary endpoints 6 and 7 will be determined by participants using questionnaires. Secondary endpoint 8 will be determined by questionnaire in all centres, and in a subset (i.e. Oxford, Guy's and St Thomas' Trusts and Royal Free Hospital Trust) using MEMS (see below).

5.2.3 Endpoint Committee

The endpoint committee will be composed of clinicians with specialist training in orthopaedic practice or infection. The endpoint committee will remain blind to allocation. The committee will have a chair and 2 other members (i.e. Ben Lipsky, chair, Deepa Bose and Harriet Hughes). If any endpoint committee member stands down during the course of the trial, they will be replaced by someone with similar background and qualifications.

Any post-randomization re-admission or return to theatre with signs or symptoms at the anatomical site of infection will be considered a potential endpoint. In addition, any signs or symptoms identified on review of the patient or their hospital notes at follow up visits that, in the opinion of the study clinician, may meet the definition of treatment failure will be considered a potential endpoint.

The hospital notes relating to the inpatient admission or outpatient visit for the potential endpoint will be redacted by the local clinician for a) personal identifiable information and b) specifics of antibiotic treatment and/or line insertion, which may indicate the route of administration of antibiotics.

These redacted notes will be forwarded to the blinded endpoint committee, who will determine whether an endpoint has been met. 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. 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 only be required to review potential treatment failure. All other secondary endpoints including SAEs, line complications, early termination of treatment and data for resource allocation will be determined directly by the local study clinicians.

The endpoint committee will also have a role in determining diagnostic sub-groups for the purposes of analysis (see analysis section, 8.13, below).

5.3 Trial Participants

5.3.1 Overall Description of Trial Participants

Participants will be considered for inclusion when an infectious disease physician reviews a patient with bone or joint infection. The contact will be triggered by routine care pathway, e.g., a referral by the team caring for the patient, a referral from primary care direct to infectious disease services, or by following up a laboratory result.

Patients may be recruited from the following hospital trusts;

Birmingham Heartlands

Bristol Royal Infirmary

Cambridge University Hospitals

Gartnavel General Hospital

Guys and St Thomas' Hospitals Trust

Hull Royal Infirmary

James Cook Hospital, Middlesborough

Leeds Teaching Hospitals Trust

Newcastle Hospitals Trust

NHS Lothian Hospitals

Oxford University Hospitals

Royal Free Hospital, London

Royal National Orthopaedic Hospital

Royal Hallamshire Hospital, Sheffield

Royal Liverpool University Hospital

Royal United Hospital Bath

Tayside University Hospitals Trust

University Hospital Southampton

Included sites currently use 6 weeks of intravenous antibiotic therapy as standard treatment for some categories of bone and joint infection, and are able to deliver intravenous antibiotics to patients after discharge from hospital. We anticipate that each site will recruit at least 20 patients per year, and therefore would need to see approximately 40 patients per year who meet eligibility criteria

In addition, the patients recruited in Oxford University Hospitals under the preliminary single-centre study (REC reference 09 H0604 109) will be included in the final analysis for this multi-centre protocol, and will complete their follow up under the multi-centre protocol.

5.3.2 Inclusion Criteria

The participant must meet each of the following inclusion criteria;

1) A clinical syndrome comprising any of the following; a) localized pain OR b) localized erythema OR c) temperature >38.0ºC OR d) a discharging sinus or wound AND
2) willing and able to give informed consent AND
3) aged 18 years or above AND
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 AND

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 OR b) Native joint sepsis treated by excision arthroplasty OR 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) OR d) Orthopaedic device or bone-graft infection treated by debridement and retention, or by debridement and removal OR e) Spinal infection including discitis, osteomyelitis and/or epidural abscess.

5.3.3 Exclusion Criteria

The participant may not enter the study if ANY one of the following applies:

1) *Staphylococcus aureus* bacteraemia on presentation or within the last 1 month OR
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) OR
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) OR
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 OR
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) OR
6) Previous enrolment in the trial OR
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) OR
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 OR
9) There is clinical, histological or microbiological evidence of mycobacterial, fungal, parasitic or viral aetiology OR
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.

5.4 Expenses and Benefits

There will be no additional study visits required as a result of participation in the trial, and hence no expenses and benefits. At the time of randomisation, study participants will be given stamped addressed envelopes in order to post questionnaires back. The questionnaires will be dated to indicate when they should be completed.

5.5 Study Procedures

5.5.1 Study Timetable

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 questionnaire
Day 0, 120, 365	Oxford Hip/Knee Questionnaire
Day 14, 42	Adherence Questionnaire

5.5.2 Informed Consent

Participants will be consented by an appropriately trained clinician or research nurse using the REC approved information sheet and consent form. The study clinician or research nurse will assess whether the patient can give informed consent or not during the consent process, in compliance with the 2005 mental capacity act. We will not recruit cognitively impaired patients who, in the opinion of the local study clinician or research nurse, are unable to give informed consent for participation in the trial. The participant will be given as much time as they require to read the sheet and consult with friends or relatives if they wish, and the study clinician or research nurse will return later if requested by the patient. The study team will strike a balance between giving adequate time to consider the study and allowing the time-window for eligibility to elapse (i.e. that ≤ 7 days of antibiotics have been given as specified above). It will be emphasized that;

- participation is voluntary, the alternative being routine clinical care
- there is uncertainty regarding the benefits and risks of oral antibiotics compared with IV antibiotics for treating bone and joint infections
- the clinic visits required for participation will be identical to those required for routine care.
- study participants will be free to change their mind at any stage
- routine clinical care will not be affected by a decision to not participate, or by a decision to withdraw from the trial at a later stage.
- Data collected during the trial may at some stage be used in further ethically approved studies of antibiotic treatment and may be shared with other researchers; this may include researchers outside of

the European Union where laws may not protect data privacy to the same extent as in the UK. To ensure confidentiality, none of the data stored or transferred electronically will contain personal identifiers.

Written informed consent is required for entry into the trial. Participants must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Study participants will be left with a copy of the information sheet and a signed consent form.

If a participant loses capacity during the trial, we will seek written assent from a consultee to allow continuing data collection from the participant's medical records.

5.5.3 Screening and Eligibility Assessment

Eligibility will be assessed by a study clinician based on a review of the clinical notes and clinical assessment. The inclusion and exclusion criteria required are listed above. No additional laboratory or other diagnostic tests will be required.

The hospital number and a sequentially assigned study number will be recorded on an enrolment log.

Culture and/or histology results are not required to confirm eligibility to the study.

5.5.4 Baseline Assessments

The study clinician will record age, gender, comorbid conditions (diabetes, renal failure, cardiovascular disease, neurological impairment, immunosuppression, rheumatoid arthritis, malignancy) and smoking history in the eCRF, and the primary diagnosis for which treatment is planned will be recorded. The clinician will also record the intended antibiotics which will be given conditional on randomisation to oral or IV antibiotics, in order to enable sub-group analysis.

In order to prevent any participant from being enrolled twice, the hospital number and date of birth will be entered into the eCRF, and an automatic check will alert the investigator to an apparent attempt at a repeat enrolment.

No additional blood tests or other investigations will be required as a result of being recruited to the study. The patient will be asked to complete an EQ-5D questionnaire and an Oxford Hip or Knee score (if either the hip or knee is affected). We will provide a stamped and addressed envelope for the patient to return the questionnaires for data entry.

5.5.5 Randomisation

A randomisation list stratified by site will be prepared by a statistician and held securely by the Oncology Clinical Trials Office (OCTO), who will provide database and randomization services support. The study clinician will contact OCTO (by telephone or via a website link) and after confirming the patient's eligibility criteria they will be assigned a sequentially allocated study number. OCTO will then confirm the randomised treatment allocation.

There will be no run-in period. The study is open label. Participants will be randomized to "strategies" (i.e. PO vs IV) for the first 6 weeks of antibiotics, rather than individual drugs (see below for details). If randomized to IV strategy, the participant will be expected to complete 6 weeks of IV antibiotics, and may or may not have

additional oral antibiotics. If randomized to the PO strategy, participants will be expected to switch from IV to PO before or at 7 days after the start of treatment. (Treatment begins either following an appropriate surgical procedure, or with the first antibiotics given after the onset of the clinical episode for which the patient is being treated.) Drugs will be prescribed and dispensed in the routine way using the hospital pharmacy prior to and on discharge, and from the GP surgery and community pharmacy after discharge.

The local clinician or study nurse will record in the patient's medical inpatient notes that they have been randomised, and leave contact details for the study team.

5.6 Subsequent assessments

While an inpatient, the study clinician and/or research nurses will maintain contact with the clinical team to identify potential endpoints, and to implement the antibiotic strategy outlined above. Antibiotic prescribing and the date of discharge will be recorded.

Following discharge, the participants will be seen according to routine policy in the local site, with investigator reviews at 6 weeks (range from day 21 to day 63), 4 months (range day 70 to day 180) and 1 year (range day 250 to day 420).

If the patient does not attend clinic within the specified date range, the investigator will arrange a telephone review. They will telephone the participant and/or the participant's GP to identify endpoints or serious adverse events that may have occurred at other hospitals, and will obtain further details. If, based on the telephone discussion, an outpatient attendance or admission is clinically indicated, the investigator will organise this and advise the patient accordingly.

A study clinician will review the source documents from routine care visits when completing investigator reviews. They will record;

a) Microbiology and histology results and date of discharge (first review only)
b) The frequency of outpatient visits since randomization
c) Severe adverse events to date
d) And re-admissions for inpatient care (whether SAEs or not)
e) the type of line used and any line complications
f) episodes of C Diff Associated Diarrhoea
g) Antibiotic use to date (including mode of delivery – i.e. district nurse, self administered or by regular clinic visits)
h) Presence/ absence of Potential Endpoints
i) The reason for not completing the planned antibiotic course (if applicable).

There will be no routine monitoring of solicited or unsolicited adverse events that do not meet the criteria for SAEs.

5.6.1 Questionnaires

The patient will be asked to complete EQ-5D and adherence questionnaires to assess quality of life and adherence to antibiotics according to the timetable above. These questionnaires will be handed out with stamped addressed envelopes, and labelled with the dates that their return is expected on.

In addition, an EQ-5D will be requested on the occasion of any SAE that the investigators believes is probably or definitely linked to antibiotics received in the first 42 days (i.e. when treatment is randomized), or any admission to hospital with a potential endpoint, in order to evaluate the impact on the patient. The local site investigators will ensure that a questionnaire is given to the patient, which the patient will be asked to complete and return for data entry.

5.6.2 MEMS (Medication Event Monitoring Systems) for adherence

In a subset of sites (i.e. Oxford, Guys and St Thomas' Hospitals Trust and Royal Free Hospital Trust), pharmacy departments will dispense oral antibiotics in pill containers with a Medication Event Monitoring System (MEMS). This method of monitoring has become standard in studies of medication where adherence is critical [27,28]. Sensors in the pill bottle tops detect opening and closing, and record these events with a date stamp. The sensors can be read at a later date, and therefore we can verify whether patients opened and closed their bottles at times that are consistent with their prescription.

If more than one antibiotic is prescribed, we will use the MEMS sensors on the more frequently dosed antibiotic. If changes to antibiotic prescriptions are required after discharge, this will usually take place out-of-hours or at short notice in the community and the hospital pharmacy will not usually be able immediately to dispense replacements using MEMS.

The MEMS sensors will be collected and read at the next clinic visit after completion of the course in order to document how often the containers have been opened. The summary data on doses completed will then be entered in the eCRF by the local investigator.

5.7 Definition of End of Trial

The end of trial will be the day 365 visit follow-up of the last patient to be enrolled

5.8 Discontinuation/ Withdrawal of Participants from Study Treatment

Participants are eligible for entry to the study based on the available clinical information. If infection is not confirmed subsequently (see inclusion criteria above), or if the randomly allocated oral or IV strategy is subsequently judged to be clinically inappropriate and therefore cannot be completed, then the study participant will continue follow up in the trial. They will be included in the "intention to treat" analysis, but will not be included in "according to protocol" analysis. Routine clinical care consistent with the new information will be recommended.

Each participant has the right to withdraw from the study at any time. If a participant withdraws from the study during the randomized treatment phase, they will be offered routine clinical care. They will still be included in intention to treat analysis.

During the randomized treatment phase the investigator may discontinue a participant from the randomized therapy if it is not compatible with good clinical care. Details are given below under PO antibiotic strategy and IV antibiotic strategy. Follow up will continue. Discontinuation from follow up will only occur if the participant requests it. The data obtained to date will then be analysed as "intention to treat" but not "according to protocol". The reason for discontinuation of treatment will be recorded in the CRF.

5.9 Source Data

The eCRF reviews will be completed directly by the study clinician reviewing the patient (by web-based electronic data entry), and not transcribed later.

The eCRF will specify whether the data entry is based on review of the patient records made by another clinician, by telephone contact, or by direct observation.

The eCRF will be stored separately from the patient record, but the investigators will ensure all clinically relevant information is in the patient record. If, for any reason (including endpoint committee reviews), copies of patient records are needed for review outside of the patient's clinical care team, then personal identifying information will be covered on photocopying and the photocopies labelled with the participant number.

6 TREATMENT OF TRIAL PARTICIPANTS

6.1 Description of Study Treatment: PO vs IV antibiotic strategy

To be enrolled in the study, the patient must have completed 7 days or less of intravenous antibiotic therapy after appropriate surgery (i.e. not including pre-operative antibiotics), or, if no surgery is undertaken, the patient must have completed 7 days or less of intravenous antibiotic therapy after the start of treatment for the clinical episode in question.

Following randomization, 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).

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.

6.2 Storage of Study Treatment

The antibiotics are all routinely available in the hospital pharmacies, and will be stored in the usual way.

6.3 Compliance with Study Treatment

Compliance will be documented by patient questionnaire, using questions on numbers of doses missed during a week and during the last 24 hours.

6.4 Accountability of the Study Treatment

Not applicable.

6.5 Concomitant Medication

Only antibiotic prescribing will be recorded. Additional PO antibiotics for other indications or as adjunctive treatment (e.g. the addition of oral rifampicin to IV antibiotics) will be allowed in both groups.

6.6 Post trial treatment

Participants will continue with normal care. No particular arrangements will be required as a consequence of participating in the study.

7 SAFETY REPORTING

The MHRA Clinical Trial Helpline has advised that the trial is not a Clinical Trial of an Investigational Medical Product as defined by the EU Directive 2001/20/EC and therefore no MHRA approval is required. The safety reporting section here therefore refers to our own procedures for recording adverse events and limited expedited reporting to the sponsor.

7.1 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence (i.e. not necessarily linked to medication, randomized or otherwise) that:

- Results in death OR
- Is life threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) OR
- Requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation. Planned admissions to hospital, for instance for elective surgery, are not considered SAEs OR

- Results in persistent or significant disability/incapacity OR
- Is a congenital anomaly/birth defect OR
- Other important medical events. Other events may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above.

Episodes of potential treatment failure which are forwarded to the endpoint committee for review will not be considered SAEs.

7.2 Procedures for SAEs

We will record all SAEs identified during the first year after randomisation. Data will include a description, dates of onset and resolution, severity, assessment of relatedness to randomized antibiotic strategy, whether the SAE is expected or unexpected, and other suspect drugs or devices and action taken.

7.3 Procedures for the reporting of SAEs to local R&D and REC

We will not undertake expedited reporting of SAEs (see below for definitions), since the antibiotics to be used in the trial are all licensed agents with well described safety profiles. All SAEs will be recorded in the CRF as described above.

Expected SAEs are defined as follows;

1) Complications of bone/joint surgery.
2) Complications of the bone or joint infection that the patient is undergoing treatment for (including potential endpoints).
3) Drug reactions already detailed in the product literature (i.e. the SMPCs and/or British National Formulary).
4) Drug reactions already detailed in the product literature (i.e. the SMPCs and/or British National Formulary) for concurrent medications given for routine clinical care.
5) Inter-current illness causally related to comorbid conditions that the investigator believes are likely diagnoses given the patient's history, age and other factors.

The investigator will use their judgement, such that SAEs technically meeting definitions above, but that seem unexpected in terms of severity, duration or other factors may be regarded as unexpected.

If an investigator becomes aware of an unexpected SAE during the trial, then they will report this to the CI or delegate (i.e. the trial physician) within 1 working day using fax number 01865 227671. In addition, they will make telephone contact with the CI or their delegate to alert them to the report. The CI (or their delegate) will discuss the SAE with the investigator to clarify clinical details if required, and will then be responsible for reporting the unexpected SAE within a further working day to the OUH R&D Department.

7.4 Annual Safety Reports

We will be examining the non-inferiority of different routes of administration of widely used, licensed antibiotics to treat infection. A Clinical Trials Authorisation is not required; therefore, we will not write developmental safety update reports.

7.5 Safety Reporting to DMC and Research Ethics Committee

If, in the opinion of the CI or the Sponsor, an unexpected SAE may be relevant to participant safety, then a detailed report will be prepared including an assessment of causality and severity and forwarded to the DMC. The DMC will be asked to make a recommendation regarding the safety of the trial in the light of this report.

A report will also be submitted to the REC that gave a favourable opinion of the study. This report will be submitted within 15 days of the CI (or delegate) becoming aware of the event, and will use the NRES report of serious adverse event form as currently available on the NRES website.

8 STATISTICS

8.1 Power 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, and to ensure that the "according to protocol" analysis retains reasonable power, we will aim to recruit 1050 participants.

8.1.1 Analysis of Safety

SAEs will be tabulated by treatment allocation.

8.1.2 Analysis of Efficacy

8.1.2.1 Primary Endpoint

Based on intention to treat, 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 90% confidence intervals around the absolute unadjusted difference (i.e. oral-intravenous) is less than 5%, then the criteria of non-inferiority will be met.

8.1.2.2 Secondary Endpoints

Secondary analyses will include (i) a per-protocol analysis based on all participants who have received at least 4 weeks of randomised therapy, and, if in the PO group, did not exceed the limits set for length of IV antibiotics (see above), and (ii) ITT and per-protocol analyses in the subgroup with "definitive" or "definitive" / "probable" infection at randomisation. These secondary analyses will focus on consistency of point estimates and 95% CI rather than formal comparison with the 5% non-inferiority margin. We will similarly compare the proportions of participants with secondary endpoints, or the distributions of continuous secondary outcomes (ranksum tests) as defined below. Sub-group analyses will use interaction tests to determine the consistency of treatment effects by type of infection and infecting pathogen. In some centres, randomization to oral antibiotics will result in an increased use of antibiotics with particular properties in penetrating biofilms, such as rifampicin. We will record treatment intentions for both intravenous and oral routes at baseline before randomization. Subgroup analysis will compare efficacy of intravenous versus oral antibiotics according to whether (or not) rifampicin was an antibiotic choice for intravenous and oral arms (4 subgroups). We will also conduct subgroup analyses according to the clinician's specific antibiotic intentions recorded prior to randomization, to assess whether bias exists in terms of specific patients not following their intended treatment plan after randomization.

A survival analysis will be performed to assess post-randomisation surveillance bias, which would present as a delay in time to meeting an endpoint in one randomised group. Other secondary analyses will include regression models (logistic (binary) or quantile (continuous)) to calculate estimates of treatment differences for the primary and secondary endpoints adjusted for age, comorbidity, infecting pathogen, and type of infection.

8.1.2.3 Adherence

We will describe adherence to oral medication using data from the questionnaires (full cohort) and the MEMS data in 3 centres, particularly considering the number of days on which all doses were missed, and dosing intervals in the latter.

8.1.3 Diagnostic sub-group definitions

The clinical diagnostic inclusion criterion means the trial will reflect real-world practice, and will facilitate timely entry to the study.

However, in analysis we will use histology, microbiology and clinical details to determine "definitive" evidence of infection, defined by; a) isolating bacteria from 2 or more samples of bone/spine/peri-prosthetic tissue, where the bacteria are similarly typed OR b) a pathogenic organism (e.g. *Staphylococcus aureus* but not *Staphylococcus epidermidis*) on a single, closed, biopsy of native bone or spine OR c) diagnostic histology on bone/peri-prosthetic tissue OR d) a draining sinus tract arising from bone/prosthesis or 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.

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.

The endpoint review committee will be blinded to treatment allocation and subsequent outcome. Secondary analysis will evaluate non-inferiority for "definitive" or "definitive"/ "probable" infections only.

8.1.4 Health Economic Analysis

The health economic evaluation will comprise two parts. In the first part, a within trial analysis will be performed based on the resource use and Health Related Quality of Life (EQ5D) data collected in OVIVA. We will use the BNF for antibiotic costs (with a sensitivity analysis for hospital pharmacy discounts). We will include the costs associated with IV administration based on staffing requirements, equipment cost, clinic visits and transport costs for patient visits as observed in the trial. For unplanned inpatient stays and additional outpatient attendances other than those related to IV administration, we will use standard NHS reference costs.

We will calculate mean costs in each arm of the trial and differences in costs between the two arms, with 95% confidence intervals. The EQ-5D instrument will be used to estimate per-patient quality-adjusted life years

(QALY) with adjustment for any differences between the groups in EQ5D at baseline. Non-parametric bootstrapping techniques will be employed to confirm the robustness of the statistical analysis of cost, QALY and cost-per-QALY. Uncertainty in cost-effectiveness will be represented on the cost-effectiveness plane and as confidence intervals for cost-effectiveness ratios, or as cost-effectiveness acceptability curves, as appropriate.

The second part of the analysis will be to extrapolate the observed results in OVIVA beyond the clinical trial, in order to explore the potential lifetime cost-effectiveness of a switch in antibiotic strategy. This extrapolation will be made in each diagnostic group, using estimates of long-term recurrence from the literature, and the observed recurrence rates observed within the period of the trial. We will also use the published longer-term costs associated with disability, in order to reflect the consequences of treatment failure that persist beyond the end of the trial. Taking these estimates together, we will extrapolate the costs beyond the period of observation within the year of follow up in the trial. This will necessarily involve a series of assumptions in applying estimates from the literature, and extensive sensitivity analyses will be examined in order to explore the robustness of the estimates.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

We will conduct remote monitoring of data entered in real time. The chief investigator will ask local investigators to confirm unusual values, and will undertake monitoring visits if there are concerns regarding the integrity of data that cannot be resolved remotely.

10.1 Data Monitoring Committee

A data safety monitoring board will be formed. The DMC will be composed of 3 members; Neil French (chair, Professor of Infectious Disease, Liverpool University), Tim Peto (NIHR senior investigator and statistician, Oxford) and Martin Llewelyn (Brighton and Sussex University). We recognise the potential for apparent conflict of interest in having a DMC member based in Oxford (i.e. TP). We believe the conflict of interest to be minimised by TP not having any role on the Bone Infection Unit in Oxford, and therefore no contact with the trial procedures. On the other hand we believe there are advantages in including TP as a senior NIHR investigator with combined expertise in infectious disease, clinical trial design and statistics, and also as a highly experienced DMC member. TP has acted as DMC member for the preliminary single-centre OVIVA run since it began, and we believe his continuity of involvement will be a further advantage to the trial.

If, during the course of the trial, one of the DMC members withdraws, we will identify a replacement with a similar background. The DMC will review the analysis plan, and their approval will be required before it can be implemented. The DMC will receive reports regarding unexpected SAEs, and will review the final study report. The DMC will be empowered to advise stopping or suspending the trial.

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. The DMC will also, on the basis of this review, determine a requirement for a further interim review during the course of the trial.

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).

If the study is below 50% of the projected recruitment rate after 10 months then, after appropriate discussion with the TSC, the CI will ask the DMC to review endpoint data, to reconsider the projected power of the study given the frequency of endpoints identified, and to make a recommendation regarding stopping the trial on grounds of futility if appropriate.

The DMC will meet to discuss the analysis plan before the investigators conduct the final analysis. The investigators will participate in part of these meetings, but the DMC will complete the meeting without an investigator presence before coming to a final view. 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.

10.2 Trial Steering Committee

A trial steering committee will be formed. The trial steering committee will have an independent chair (Graham Cooke, Imperial college London), and co-chair (John Paul, health protection agency). In addition, the TSC will have two public/ patient group representatives (Fraser Old, Nuffield Orthopaedic Centre Network and Jennifer Bostock, Healthcare-Associated Infection Service Users Research Forum), two Oxford Clinical Trials Unit directors (David Beard, deputised where necessary by Cushla Cooper, Trials Manager, OSIRIS and Rachel Midgley, OCTO), statistician (Ines Rombach, OSIRIS) and the chief investigator. If a member of the TSC withdraws during the course of the trial, we will identify a replacement with a similar background.

The Trial Steering Committee will meet at the start of the trial, and then yearly to review recruitment rates, protocol amendments, any protocol deviations identified, and may make recommendations to the sponsor regarding running the trial.

11 ETHICS

All clinicians involved in the study have acknowledged a position of equipoise in relation to treatment for bone and joint infections; they accept that there is currently insufficient evidence to determine whether oral antibiotics are inferior to intravenous antibiotics in this context. This uncertainty will be conveyed to patients both verbally at study introduction and in writing via the patient information sheet.

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

11.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) and host institutions R&D committees for written approval. Annual progress reports will be submitted to OUH R&D and to the appropriate REC.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants local hospital number and study number on the electronic CRF. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so. Data may be used for further ethically approved studies of antibiotic treatment and may be shared with other researchers; this may include use of data outside the European Union where laws may not protect data privacy to the same extent as in the UK. To ensure confidentiality, none of the data stored or transferred electronically will contain personal identifiers.

12 DATA HANDLING AND RECORD KEEPING

All data entry at the sites will be electronic. The patients will return questionnaires, using the stamped addressed envelopes provided on randomisation. The results of endpoint committee reviews will be kept on paper, stored by the chief investigator or their delegate, and the results of these endpoints will be entered by the trial physician into a second database, held separately, for which access will be restricted to the trial physician, statistician, and DMC. This database of endpoints will only be merged with the main trial database (which includes treatment allocations) at the end of the trial, or at the request of the DMC. Investigators will not undertake any interim analyses using these data, either on a site-specific basis or for the whole trial.

13 FINANCE AND INSURANCE

The trial investigators are all NHS employees, covered by the standard NHS indemnity. The study will be sponsored by the OUH, and reviewed by the R&D department prior to starting, to ensure that appropriate indemnities are in place.

The running costs of the trial are funded by the NIHR HTA.

14 PUBLICATION POLICY

The outcome of the trial will be published in open access form. The DMC will review a manuscript before submission for publication, and authorship will be according to the ICJME criteria.

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16 APPENDIX A: EQ-5D QUESTIONNAIRE

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

Mobility

I have no problems in walking about □

I have some problems in walking about □

I am confined to bed □

Self-Care

I have no problems with self-care □

I have some problems washing or dressing myself □

I am unable to wash or dress myself □

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

I have no problems with performing my usual activities □

I have some problems with performing my usual activities □

I am unable to perform my usual activities □

Pain/Discomfort

I have no pain or discomfort □

I have moderate pain or discomfort □

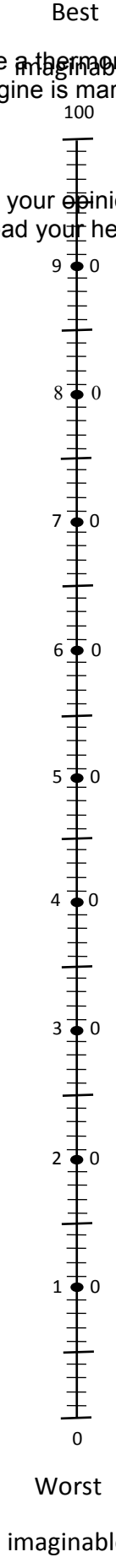
I have extreme pain or discomfort □

Anxiety/Depression

I am not anxious or depressed	□
I am moderately anxious or depressed	□
I am extremely anxious or depressed	□

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line to whichever point on the scale indicates how good or bad your health state is today.



17 APPENDIX B: COMPLIANCE QUESTIONNAIRE

(Source: Morisky Adherence Measure Questionnaire)

You indicated that you are taking antibiotics medication for your bone or joint infection.

We are interested in your experience of taking your medication. There is no right or wrong answer. Please answer each question based on your personal experience.

1. Do you sometimes forget to take your antibiotics? YES NO

2. People sometimes miss taking their antibiotics for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your antibiotics?
YES NO

3. Have you ever cut back or stopped taking your antibiotics without telling your doctor, because you felt worse when you took it? YES NO

4. When you travel or leave home, do you sometimes forget about your antibiotics?
YES NO

5. Did you take your antibiotics yesterday? YES NO

6. When you feel like your infection is under control, do you sometimes stop taking your medicine?
YES NO

7. Taking antibiotics is a real inconvenience. Do you ever feel stressed about sticking to your antibiotic treatment plan? YES NO

8. How often do you have difficulty remembering to take all your medications? (Please circle the correct answer)

Never/Rarely Once in a while Sometimes Usually All the time

18 APPENDIX C: OXFORD HIP/KNEE SCORE QUESTIONNAIRE

1. Describe the pain you usually have from your hip/knee (Circle one that best applies).

a) None b) Very mild c) Mild
d) Moderate e) Severe

2. Have you had any trouble washing and drying yourself (all over) because of your hip/knee? (Circle one that best applies)

a) No trouble at all b) Very little trouble c) Moderate trouble
d) Extreme difficulty e) Impossible to do

4. Have you had any trouble getting in and out of the car or using public transport because of your hip/knee? (With or without a stick)

a) No trouble at all b) Very little trouble c) Moderate trouble
d) Extreme difficulty e) Impossible to do

5. For how long are you able to walk before the pain in your hip/knee becomes severe? (With or without a stick)

a) No pain or more than 60 minutes b) between 6 and 60 minutes c) 1 to 6 minutes
d) After walking around the house e) Severe pain on any walking

6. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip/knee?

a) Not at all painful b) Slightly painful c) Moderate pain
d) Very painful e) Unbearable pain

7. Do you limp when you walk because of your hip/knee?

a) Rarely/never b) Sometimes or just at first c) Often, not just at first
d) Most of the time e) All of the time

8. Could you hip/kneel down and get up again afterwards?

a) Yes, easily b) With little difficulty c) With moderate difficulty
d) With extreme difficulty e) No, impossible

9. Are you troubled by pain in your hip/knee at night in bed?

a) Not at all b) Only one or two nights c) Some nights
d) Most nights e) Every night

10. How much has pain from your hip/knee interfered with your usual work? (including housework)

a) Not at all b) A little bit c) Moderately
d) Greatly e) Totally

11. Have you felt that your hip/knee might suddenly "give away" or let you down?

a) Rarely/Never b) Sometimes or just at first c) Often
d) Most of the time e) All the time

12. Could you do household shopping on your own?

a) Yes, easily b) With little difficulty c) With moderate difficulty
d) With extreme difficulty e) No, impossible

13. Could you walk down a flight of stairs?

a) Yes, easily b) With little difficulty c) With moderate difficulty
d) With extreme difficulty e) No, impossible

FINALPROTOCOL

STUDY TITLE: RANDOMIZED OPEN LABEL STUDY OF ORAL VERSUS INTRAVENOUS ANTIBIOTIC TREATMENT FOR BONE AND JOINT INFECTIONS REQUIRING PROLONGED ANTIBIOTIC TREATMENT: MULTI-CENTRE STUDY.

Internal Reference No: NCT00974493

Research Ethics Committee Ref: 13/SC/0016 South Central Oxford REC B

Date and Version No: Version 2, 1st May 2015

Chief Investigator:	Matthew Scarborough (Oxford University Hospitals) Matthew.scarborough@ouh.nhs.uk Tel 0787 2436461
Investigators:	Philip Bejon (Oxford University Hospitals) Guy Thwaites (Guys and St Thomas' Hospital London) Hemant Pandit (Oxford University Hospitals) Martin McNally (Nuffield Orthopaedic Centre) David Beard (Oxford University, Trials Unit Director) Cushla Cooper (Oxford University, Trial manager) Andrew Seaton (Gartnavel General Hospital, site PI) Andy Briggs (Glasgow University, Health economics analysis) Rachel Midgley (Oncology Clinical Trials Office) Carolyn Hemsley (Guys and St Thomas' Hospitals, site PI) Jonathan Sandoe (Leeds Teaching Hospitals Trust, site PI) Jonathon Folb (Royal Liverpool University Hospital, site PI) Claire Mackintosh (NHS Lothian, site co-PI) Becky Sutherland (NHS Lothian, site co-PI) Susan Hopkins (Royal Free Hospital, site PI) Damien Mack (Royal Free Hospital, site PI) Simon Warren (Royal National Orthopaedic Hospital, site PI) Martin Williams (Bristol Royal Infirmary, site PI) Neil Jenkins (Birmingham Heartlands, site PI)

	Gavin Barlow (Hull Royal Infirmary, site PI) Uli Schwab (Newcastle Hospitals Trust, site PI) Ila Aggarwal (Tayside University Hospitals Trust, site co-PI) Elinor Moore (Cambridge University Hospitals, site PI) Julia Greig (Royal Hallamshire Hospital, Sheffield, site PI) Jon Campion (Northampton General Hospital) Nick Nicolaou (Tunbridge Wells Hospital, Pembury, Kent) Catherine Sargent (Brighton and Sussex Hospitals PI) Mel Newport (Brighton and Sussex Hospitals, co PI) Simon Ellis (Wansbeck Hospital, Northumbria) Caroline Barker (Norfolk and Norwich Hospitals, site PI) Bijayendra Singh (Medway Maritime Hospital, site PI) Ian Dos Remedios (University Hospitals of North Midlands, site PI) Neena Bodasing (University Hospitals of North Midlands, co PI) Parvez Moondi (Queen Elizabeth Hospital, King's Lynn), PI) Rashmi Sharma (Blackpool NHS Foundation Trust, site PI) Sarah Meisner (Royal United Hospital Bath NHS Trust, site PI) Jim Buckley (North West London Hospitals NHS Trust, site PI) Michael Kelsey (Wittington Hospitals NHS Trust, site PI) Benjamin Lipsky (Endpoint committee chair) Deepa Bose (Endpoint committee) Harriet Hughes (Endpoint committee) Ines Rombach (Oxford University, statistician) Sarah Walker (Oxford University, senior statistician)
Sponsor:	Oxford University Hospitals NHS Trust
Funder:	NIHR HTA programme Biomedical Research Centre (salary support)

Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

Principal Investigator	Investigator Signature	Date
(Print Name)		

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

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AMENDMENT HISTORY

Amendment No.	Protocol Version No.	**Date issued**	**Author(s) of changes**	**Details of Changes made**
1	1.3	11.01.13	M Scarborough	University Hospital Southampton added as a site, and the Royal Free and Royal National Orthopaedic Hospitals listed as independent sites (5.3.1) Provision for signed assent in the event that a patient loses capacity during the trial.
2	1.3	11.01.13	M Scarborough	(5.5.2) Provision for potential data transfer outside the EU (5.5.2 and 11.4)
3	1.3	11.01.13	M Scarborough	Inclusion with the PIS, an invitation letter from clinicians responsible for participants
4	1.3	11.01.13	M Scarborough	Amendment to the membership of the DMC and TSC to comply with recommendations of the HTA (10.1 and 10.2)
5	1.4	01.07.2013	M Scarborough	Provision for continuing validity of fully informed consent at Scottish sites in the event of a participant subsequently loosing capacity during the trial. (5.5.2)

6	1.4	01.07.2013	M Scarborough	Provision for use of NHS number as the primary identifier in order to accommodate electronic randomisation and variation of local practice with respect to use of hospital identifiers (5.5.4 and 11.4) Inclusion of additional sites to the trial
7	1.5	20.01.14	M Scarborough	Facility for MEMS cap bottles to be prepared by ward pharmacists and trial staff (5.6.2) 12 months extension to recruitment Amendment of participating sites (5.3.1)
8	1.5	20.01.14	M Scarborough	Facility for MEMs monitoring at additional sites (5.6.2)
9	1.5	20.01.14	M Scarborough	Amendment of participating sites (5.3.1) Correction of typographical and copy errors (2 and 8.1.3)
10	1.6	30.09.14	M Scarborough	Adjustment of non-inferiority margin (8.1)

11	1.6	30.09.14	M Scarborough	Addition of limited qualitative study to investigate barriers to recruitment – *[submitted as a separate, independent study]*
12	1.6	30.09.14	M Scarborough	Present the Oxford Hip score and Oxford Knee score as separate appendices (18, appendix Ci and ii)
13	2	01.05.15	M Scarborough	
14	2	01.05.15	M Scarborough	
15	2	01.05.15	M Scarborough	
16	2	01.05.15	M Scarborough	
17	2	01.05.15	M Scarborough	

19 SYNOPSIS

Study Title	Randomized open label study of oral versus intravenous antibiotic treatment for bone and joint infections requiring prolonged antibiotic treatment: Multi-centre study.
Internal ref. no.	
Clinical Phase	Phase IV
Trial Design	Open label, randomized non-inferiority trial
Trial Participants	Inpatients in the NHS trusts taking part in the study (see list in protocol) who are referred for a prolonged course of antibiotic therapy for bone and joint infections.
Planned Sample Size	1050
Follow-up duration	1 year
Planned Trial Period	3 years, extended to 28th February 2017. 12 month extension approved by the HTA
Primary Objective	To determine whether oral antibiotics are non-inferior to intravenous antibiotics for serious bone and joint infection, judged by numbers meeting a primary, objective endpoint for definitive treatment failure during 1 year of follow up.
Secondary Objectives	To determine the percentage of patients completing allocated treatment (i.e. oral or intravenous), cost-effectiveness of treatment, safety judged by incidence of severe adverse events and efficacy judged by the frequency of secondary endpoints for efficacy.
Primary Endpoint	Definite failure of infection treatment, defined by objective criteria (specified in detail in the protocol) and determined by blinded endpoint committee review.
Secondary Endpoints	10. Serious adverse events, including death (all cause) 11. Line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line). 12. *Clostridium difficile* associated diarrhoea 13. Probable and possible treatment failure defined in detail in the protocol, and determined by blinded endpoint committee review. These secondary endpoints will be analysed as composites of a) definitive and/or probable; or b) definitive and/or probable and/or possible recurrent infection. 14. Early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason. 15. resource allocation assessed using; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs. 16. Quality of life evaluated by EQ-5D questionnaire 17. Oxford Hip and Knee Scores (where infection is in the hip or

	knee), a Patient Reported Outcome Measure selected by the Dept. of Health for evaluating outcome after orthopaedic surgery. 18. Adherence to taking medication.
Investigational Medicinal Products	None. Oral versus intravenous antibiotic prescribing strategy will be determined by randomization, but not individual agents.

20 ABBREVIATIONS

Add or delete as appropriate.

AE	Adverse event
AR	Adverse reaction
BJI	Bone and/or Joint Infection
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
eCRF	Electronic Case Report Form
EQ-5D	EuroQol 5 dimensions health economic survey instrument
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
ITT	Intention to treat
IV	Intravenous
MEMS	Medication Event Monitoring System (i.e. sensors to detect pill bottle opening and closing)
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
OCTO	Oncology Clinical Trials Office
OPAT	Outpatient Parenteral Antibiotic Therapy
OUH	Oxford University Hospitals NHS Trust
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PO	Per Oral
R&D	NHS Trust R&D Department
REC	Research Ethics Committee

SAE	Serious Adverse Event
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

21 BACKGROUND AND RATIONALE

Bone and joint infections are common in the UK. In the NHS, 100,000 primary joint replacements and 20,000 femoral neck and long bone repairs are performed each year. Infection of bone or joint complicates around 2000 (2.0%) of these procedures, resulting in disproportionately increased mortality, disability and suffering. Treating these infections costs the NHS £20,000 to 40,000 per patient. In addition, osteomyelitis complicates 20% of foot ulcers in diabetic patients, with an incidence of 0.2% per year, translating to 5,000 episodes per year within the NHS.

A prolonged course (4-6 weeks) of intravenous antibiotics therapy delivered by the intravenous (IV) route is considered the "gold standard" treatment for bone and joint infections [1-3]. The inconvenience and cost of prolonged intravenous antibiotics can be reduced by outpatient antibiotic therapy (OPAT) programmes, and patients with bone or joint infection make up a large proportion of the patients treated by OPAT programmes [4-9]. Many hospitals in the UK lack such programmes, and the cost and risk to the patient is higher if prolonged IV therapy is delivered as an inpatient [6].

However, the evidence base supporting the need for prolonged intravenous antibiotic therapy is, in fact, limited.

Randomized controlled trials have shown that early switches to oral antibiotics are as effective as continued intravenous antibiotics for 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 randomized controlled trials of oral versus intravenous antibiotics for bone and joint infection. A Cochrane review of 8 small trials was able to include 180 participants in a comparison of intravenous versus oral therapy, and concluded there was no evidence of superiority of either treatment [15]. The largest single trial in this meta-analysis comprised 59 patients, and hence these studies have not led to a widespread change in practice in favour of oral antibiotics.

Trials demonstrate high success rates with oral antibiotics for osteomyelitis [16,17] or following an early switch to oral antibiotics for prosthetic joint infection [18]. Larger observational studies have been conducted, and report high success rates among patients treated for prosthetic joint infection with 2 stage surgical revisions with a shortened course of intravenous antibiotics or with insertion of antibiotic cement spacers [19,20].

However, observational comparisons are problematic because it is impossible to exclude "confounding by indication", whereby only patients with better underlying prognosis are switched to oral antibiotics, and do well because of their underlying prognosis, not the oral antibiotics.

There is in vivo and in vitro evidence that highly bioavailable combinations of oral therapy with fluoroquinolones and rifampicin are particularly active in prosthetic joint associated infection [21] and osteomyelitis [22]. More limited data suggests oral fusidic acid-rifampicin combinations may have similar properties [23].

The risks of IV catheter-related infections, vein thrombosis and adverse reactions to the antibiotic agents are well described [5,24]. Oral antibiotic therapy may reduce risk, be more convenient for the patient and less costly. Against this, oral therapy carries the risks of poor adherence, gastro-intestinal intolerance, poor bioavailability of some agents, and the acquisition of antibiotic resistance (e.g. rifampicin [25] or fusidate [26]).

For the majority of bone and joint infections currently treated by OPAT, an oral antibiotic regimen with high oral bioavailability, good tissue penetration and exhibiting activity against the known or likely pathogens may be effective. This strategy, however, has not yet been compared to intravenous treatment in clinical trials involving patients with the common types of infections for which prolonged intravenous antibiotic therapy is commonly prescribed.

We began a pilot study in June 2010 (Study Title: Randomized open label study of oral versus intravenous antibiotic treatment for bone and joint infections requiring prolonged antibiotic treatment: Preliminary study in a single centre, Ethics Ref: 09/H0604/109, Eudract Number: 2009-015744-42). At the time of writing, 24th September 2012, we have recruited 197 patients, and identified 10 primary endpoints and 20 serious adverse events.

We will include the patients from this pilot study in the analysis of the multi-centre trial, and patients who have not completed follow up at the point of beginning the multi-centre trial will complete their follow up under the multi-centre trial protocol.

21.1 3.1 Rationale for study

Among the patient groups eligible for this study, 6 weeks of IV therapy is the current standard of care in the hospital trusts taking part in the study. The objective of the study is to compare the efficacy and safety of intravenous versus oral antibiotic therapy for patients with bone and joint infection.

Antibiotics suitable for IV use are often not suitable for oral use (because they are not absorbed), and oral antibiotics are often not suitable for IV use (because they tend to need more frequent dosing than is logistically desirable with outpatient IV therapy). It is therefore not appropriate simply to randomize the route of administration without this affecting the choice of antibiotic. Furthermore, the choice of antibiotic is subject to patient factors, the organism cultured and the site of infection, and the preferred antibiotic may change during treatment as laboratory results are returned or the patient experiences drug reactions. Hence, it is not feasible to develop a protocol specifying anticipated management decisions to cover all eventualities for either IV or oral antibiotic choice.

In this study, we will therefore randomize participants to an oral or IV “strategy,” rather than to specific individual antibiotics. The choice of individual antibiotics within the randomized strategy will be made by a clinician trained in managing infection. He/she will consider their bioavailability, side effect profile, spectrum of activity, and, while waiting for culture results, patient risk factors for resistant organisms.

21.2 3.2 Minimising Bias

Blinding is not possible, since we consider giving a prolonged intravenous placebo treatment to be unethical. Open label studies are at risk of bias. We have therefore described objective criteria for meeting the primary endpoint, 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. The endpoint committee will determine the endpoint blind to treatment allocation.

22 OBJECTIVES

22.1 4.1 Primary Objective

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.

22.2 4.2 Secondary Objectives

To compare the following endpoints according to treatment allocation;

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

23 TRIAL DESIGN

23.1 5.1 Summary of Trial Design

The trial will be a randomized controlled open label trial of PO versus IV antibiotics. The choice of antibiotic will be left to the clinician caring for the patient, hence the trial compares strategies of antibiotic prescribing (i.e. PO versus IV) rather than individual drugs or specified combinations of drugs. The antibiotic prescribed will be chosen according to the available clinical and microbiological data, in conjunction with local antibiotic guidelines, and will be altered according to good clinical care as new results and clinical information become available. During the study period, a clinician with specialist training in infection will provide consultation as needed to select antibiotics and advise on management.

Patients with bone and joint infection who are referred for an infectious disease opinion will be considered for eligibility by a study clinician. The study clinician will determine if the patient meets the inclusion and exclusion criteria, and, if the patient is willing, the study clinician or a research nurse will obtain informed consent from the patient. If patients provide informed consent, the study clinician or research nurse will then record the clinical diagnosis and demographic data.

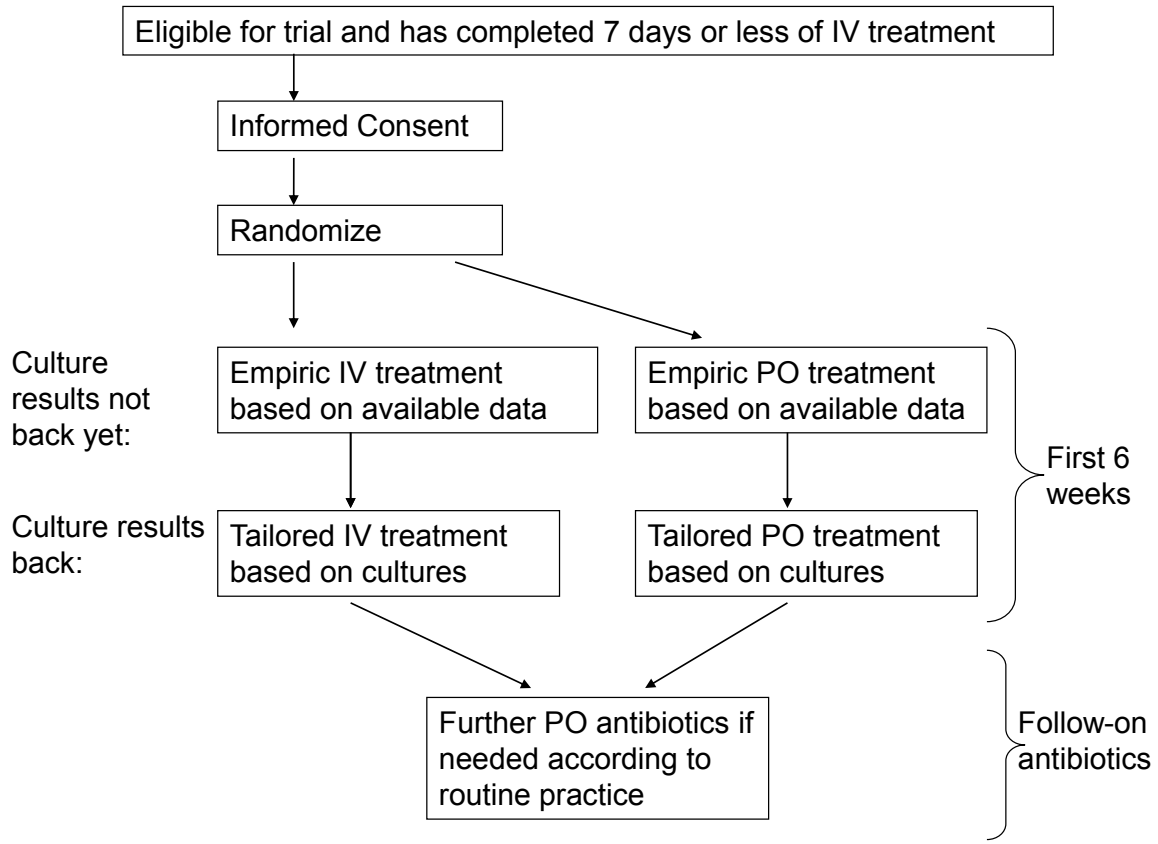
Patients may be recruited based on a clinical diagnosis of infection without microbiological results. Patients become ineligible if they have received more than one week of a planned 6-week intravenous course already. Provided the patient is eligible and gives informed consent, he/she will then be randomized to complete the first 6 weeks of antibiotic therapy with the selected course of either IV or PO antibiotic therapy. The choice of antibiotic within IV or PO groups will be determined by the responsible clinician. After this first 6-week period, further "follow on" oral antibiotic treatment will be allowed in both randomized groups, determined by usual clinical practice. Randomization group will not determine whether "follow on" antibiotics are given, or the length of the "follow on" treatment.

Participants will be seen according to routine policy in the local site, which we anticipate to include visits at least once at ~6 weeks (i.e. day 42, accepted range 21 to 63), once at ~4 months (i.e. day 120, accepted range 70 to 180) and once at ~1 year (i.e. day 365, accepted range 250 to 420) after randomization. Where the patient does not attend for scheduled follow up, the investigator will telephone the participant and/or their GP to identify endpoints that may have occurred at another hospital.

The hospital notes relating to any inpatient admission or outpatient visit where the local clinician identifies a potential treatment failure will be redacted for a) personal identifiable information and b) specifics of antibiotic treatment and/or line insertion.

These redacted notes will be forwarded to the blinded endpoint committee, who will determine whether an endpoint has been met.

Figure 1: Summary of Trial Design



23.2 PRIMARY AND SECONDARY ENDPOINTS/OUTCOME MEASURES

Endpoints will be identified by prospective surveillance throughout the year post-randomization.

The trial is open-label. The documentation for all endpoints will therefore be reviewed by an endpoint committee, blind to the treatment group.

23.2.1 Primary

The primary endpoint will be definite failure of infection treatment, where 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 OR

b) a pathogenic organism (e.g. *Staphylococcus aureus* but not *Staphylococcus epidermidis*) on a single, closed, biopsy of native bone or spine OR

c) diagnostic histology on bone/peri-prosthetic tissue OR

d) formation of a draining sinus tract arising from bone/prosthesis or 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.

23.2.2 Secondary

Secondary endpoints will be;

9) SAEs, including death (i.e. all cause) according to treatment allocation.
10) the frequency of line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line).
11) 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".
12) early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason.
13) resource allocation determined by; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs.
14) Quality of life evaluated by EQ-5D questionnaire
15) Oxford Hip and Knee Scores (where infection is in the hip or knee)
16) Adherence to oral medication

Secondary endpoints 1, 2, 4 and 5 will be determined by study clinicians. Primary endpoints and secondary endpoint 3 will be determined by the blinded endpoint committee using redacted notes. Secondary endpoints 6 and 7 will be determined by participants using questionnaires. Secondary endpoint 8 will be determined by questionnaire in all centres, and in a subset (i.e. Oxford, Guy's and St Thomas' Trusts and Royal Free Hospital Trust) using MEMS (see below).

23.2.3 Endpoint Committee

The endpoint committee will be composed of clinicians with specialist training in orthopaedic practice or infection. The endpoint committee will remain blind to allocation. The committee will have a chair and 2 other members (i.e. Ben Lipsky, chair, Deepa Bose and Harriet Hughes). If any endpoint committee member stands down during the course of the trial, they will be replaced by someone with similar background and qualifications.

Any post-randomization re-admission or return to theatre with signs or symptoms at the anatomical site of infection will be considered a potential endpoint. In addition, any signs or symptoms identified on review of the patient or their hospital notes at follow up visits that, in the opinion of the study clinician, may meet the definition of treatment failure will be considered a potential endpoint.

The hospital notes relating to the inpatient admission or outpatient visit for the potential endpoint will be redacted by the local clinician for a) personal identifiable information and b) specifics of antibiotic treatment and/or line insertion, which may indicate the route of administration of antibiotics.

These redacted notes will be forwarded to the blinded endpoint committee, who will determine whether an endpoint has been met. 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. 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 only be required to review potential treatment failure. All other secondary endpoints including SAEs, line complications, early termination of treatment and data for resource allocation will be determined directly by the local study clinicians.

The endpoint committee will also have a role in determining diagnostic sub-groups for the purposes of analysis (see analysis section, 8.13, below).

23.3 TRIAL PARTICIPANTS

5.3.1 Overall Description of Trial Participants

Participants will be considered for inclusion when an infectious disease physician reviews a patient with bone or joint infection. The contact will be triggered by routine care pathway, e.g., a referral by the team caring for the patient, a referral from primary care direct to infectious disease services, or by following up a laboratory result.

Patients may be recruited from the following hospital trusts;

Birmingham Heartlands, Heart of England NHS Foundation Trust

Bristol Royal Infirmary University Hospitals

Cambridge University Hospitals NHS Foundation Trust

Gartnavel General Hospital, NHS Greater Glasgow and Clyde

Guys and St Thomas' Hospitals Trust

Hull and East Yorkshire NHS Trust

Leeds Teaching Hospitals NHS Trust

Newcastle upon Tyne Hospitals NHS Foundation Trust

NHS Lothian Hospitals

Oxford University Hospitals NHS Trust

Royal Free London NHS Foundation Trust

Royal National Orthopaedic Hospital NHS Trust

Royal Hallamshire Hospital Sheffield Teaching Hospitals NHS Foundation Trust

Royal Liverpool and Broadgreen University Hospitals NHS Trust

Royal United Hospital Bath NHS Trust

Tayside NHS Trust

Tunbridge Wells Hospital, Maidstone and Tunbridge Wells NHS Trust

Brighton and Sussex University Hospitals NHS Trust

Wansbeck Hospital, Northumbria Healthcare NHS Foundation Trust

Medway Maritime Hospital, Medway NHS Foundation Trust

Norfolk and Norwich Hospitals NHS Foundation Trust

Royal Cornwall Hospitals NHS Trust

Queen Elizabeth Hospital King's Lynn NHS Foundation Trust

Blackpool Teaching Hospitals NHS Foundation Trust

The North West London Hospitals NHS Trust

Calderdale and Huddersfield NHS Foundation Trust

Northampton General Hospital NHS Trust

University Hospitals of North Midlands NHS Trust

Whittington Hospital NHS Trust

Included sites currently use 6 weeks of intravenous antibiotic therapy as standard treatment for some categories of bone and joint infection, and are able to deliver intravenous antibiotics to patients after discharge from hospital. We anticipate that each site will recruit at least 20 patients per year, and therefore would need to see approximately 40 patients per year who meet eligibility criteria

In addition, the patients recruited in Oxford University Hospitals under the preliminary single-centre study (REC reference 09 H0604 109) will be included in the final analysis for this multi-centre protocol, and will complete their follow up under the multi-centre protocol.

23.3.2 Inclusion Criteria

The participant must meet each of the following inclusion criteria;

7) A clinical syndrome comprising any of the following; a) localized pain OR b) localized erythema OR c) temperature >38.0ºC OR d) a discharging sinus or wound AND
8) willing and able to give informed consent AND
9) aged 18 years or above AND
10) 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.
11) has a life expectancy > 1 year AND
12) 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 OR b) Native joint sepsis treated by excision arthroplasty OR 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) OR d) Orthopaedic device or bone-graft infection treated by debridement and retention, or by debridement and removal OR e) Spinal infection including discitis, osteomyelitis and/or epidural abscess.

23.3.3 Exclusion Criteria

The participant may not enter the study if ANY one of the following applies:

11) *Staphylococcus aureus* bacteraemia on presentation or within the last 1 month OR
12) 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) OR
13) 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) OR
14) Mild osteomyelitis, defined as osteomyelitis which, in the opinion of the clinical investigator, would not usually require a 6 week course of intravenous antibiotics OR
15) 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) OR
16) Previous enrolment in the trial OR
17) 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) OR
18) 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 OR
19) There is clinical, histological or microbiological evidence of mycobacterial, fungal, parasitic or viral aetiology OR
20) 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.

23.4 Expenses and Benefits

There will be no additional study visits required as a result of participation in the trial, and hence no expenses and benefits. At the time of randomisation, study participants will be given stamped addressed envelopes in order to post questionnaires back. The questionnaires will be dated to indicate when they should be completed.

23.5 Study Procedures

5.5.1 Study Timetable

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 questionnaire
Day 0, 120, 365	Oxford Hip/Knee Questionnaire
Day 14, 42	Adherence Questionnaire

23.5.2 Informed Consent

Participants will be consented by an appropriately trained clinician or research nurse using the REC approved information sheet and consent form. The study clinician or research nurse will assess whether the patient can give informed consent or not during the consent process, in compliance with the 2005 mental capacity act. We will not recruit cognitively impaired patients who, in the opinion of the local study clinician or research nurse, are unable to give informed consent for participation in the trial. The participant will be given as much time as they require to read the sheet and consult with friends or relatives if they wish, and the study clinician or research nurse will return later if requested by the patient. The study team will strike a balance between giving adequate time to consider the study and allowing the time-window for eligibility to elapse (i.e. that ≤ 7 days of antibiotics have been given as specified above). It will be emphasized that;

- participation is voluntary, the alternative being routine clinical care
- there is uncertainty regarding the benefits and risks of oral antibiotics compared with IV antibiotics for treating bone and joint infections
- the clinic visits required for participation will be identical to those required for routine care.
- study participants will be free to change their mind at any stage
- routine clinical care will not be affected by a decision to not participate, or by a decision to withdraw from the trial at a later stage.
- Data collected during the trial may at some stage be used in further ethically approved studies of antibiotic treatment and may be shared with other researchers; this may include researchers outside of the European Union where laws may not protect data privacy to the same extent as in the UK. To protect confidentiality, none of the data stored or transferred electronically will contain patients' names or addresses.

Written informed consent is required for entry into the trial. Participants must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Study participants will be left with a copy of the information sheet and a signed consent form.

For sites in England, if a participant loses capacity during the trial, we will seek written assent from a consultee to allow continuing data collection from the participant's medical records. For sites in Scotland, at the time of recruitment, we will seek consent to continue to collect data from medical records in the event of loss of capacity but no additional assent will be required. Patients without capacity will not themselves be expected to make returns of questionnaires relating to PROMs, EQ5D or adherence.

23.5.3 Screening and Eligibility Assessment

Eligibility will be assessed by a study clinician based on a review of the clinical notes and clinical assessment. The inclusion and exclusion criteria required are listed above. No additional laboratory or other diagnostic tests will be required.

The hospital identifier and a sequentially assigned study number will be recorded on an enrolment log.

Culture and/or histology results are not required to confirm eligibility to the study.

23.5.4 Baseline Assessments

The study clinician will record age, gender, comorbid conditions (diabetes, renal failure, cardiovascular disease, neurological impairment, immunosuppression, rheumatoid arthritis, malignancy) and smoking history in the eCRF, and the primary diagnosis for which treatment is planned will be recorded. The clinician will also record the intended antibiotics which will be given conditional on randomisation to oral or IV antibiotics, in order to enable sub-group analysis.

In order to prevent any participant from being enrolled twice, the NHS number and date of birth will be entered into the eCRF.

No additional blood tests or other investigations will be required as a result of being recruited to the study. The patient will be asked to complete an EQ-5D questionnaire and an Oxford Hip or Knee score (if either the hip or knee is affected). We will provide a stamped and addressed envelope for the patient to return the questionnaires for data entry.

23.5.5 Randomisation

A randomisation list stratified by site will be prepared by a statistician and held securely by the Oncology Clinical Trials Office (OCTO), who will provide database and randomization services support. The study clinician will contact OCTO (by telephone or via a website link) and after confirming the patient's eligibility criteria they will be assigned a sequentially allocated study number. OCTO will then confirm the randomised treatment allocation.

There will be no run-in period. The study is open label. Participants will be randomized to "strategies" (i.e. PO vs IV) for the first 6 weeks of antibiotics, rather than individual drugs (see below for details). If randomized to IV strategy, the participant will be expected to complete 6 weeks of IV antibiotics, and may or may not have additional oral antibiotics. If randomized to the PO strategy, participants will be expected to switch from IV to PO before or at 7 days after the start of treatment. (Treatment begins either following an appropriate surgical

procedure, or with the first antibiotics given after the onset of the clinical episode for which the patient is being treated.) Drugs will be prescribed and dispensed in the routine way using the hospital pharmacy prior to and on discharge, and from the GP surgery and community pharmacy after discharge.

The local clinician or study nurse will record in the patient's medical inpatient notes that they have been randomised, and leave contact details for the study team.

23.6

23.7 SUBSEQUENT ASSESSMENTS

While an inpatient, the study clinician and/or research nurses will maintain contact with the clinical team to identify potential endpoints, and to implement the antibiotic strategy outlined above. Antibiotic prescribing and the date of discharge will be recorded.

Following discharge, the participants will be seen according to routine policy in the local site, with investigator reviews at 6 weeks (range from day 21 to day 63), 4 months (range day 70 to day 180) and 1 year (range day 250 to day 420).

If the patient does not attend clinic within the specified date range, the investigator will arrange a telephone review. They will telephone the participant and/or the participant's GP to identify endpoints or serious adverse events that may have occurred at other hospitals, and will obtain further details. If, based on the telephone discussion, an outpatient attendance or admission is clinically indicated, the investigator will organise this and advise the patient accordingly.

A study clinician will review the source documents from routine care visits when completing investigator reviews. They will record;

j) Microbiology and histology results and date of discharge (first review only)

k) The frequency of outpatient visits since randomization

l) Severe adverse events to date

m) And re-admissions for inpatient care (whether SAEs or not)

n) the type of line used and any line complications

o) episodes of C Diff Associated Diarrhoea

p) Antibiotic use to date (including mode of delivery – i.e. district nurse, self-administered or by regular clinic visits)

q) Presence/ absence of Potential Endpoints

r) The reason for not completing the planned antibiotic course (if applicable).

There will be no routine monitoring of solicited or unsolicited adverse events that do not meet the criteria for SAEs.

23.7.1 Questionnaires

The patient will be asked to complete EQ-5D and adherence questionnaires to assess quality of life and adherence to antibiotics according to the timetable above. These questionnaires will be handed out with stamped addressed envelopes, and labelled with the dates that their return is expected on.

In addition, an EQ-5D will be requested on the occasion of any SAE that the investigators believes is probably or definitely linked to antibiotics received in the first 42 days (i.e. when treatment is randomized), or any admission to hospital with a potential endpoint, in order to evaluate the impact on the patient. The local site investigators will ensure that a questionnaire is given to the patient, which the patient will be asked to complete and return for data entry.

23.7.2 MEMS (Medication Event Monitoring Systems) for adherence

In a subset of sites (i.e. Oxford, Guys and St Thomas' Hospitals Trust, Royal Free Hospital Trust and Royal National Orthopaedic Hospital), oral antibiotics will be dispensed to patients in pill containers with a Medication Event Monitoring System (MEMS). This facility for MEMs monitoring may also be used at additional specified sites with local agreement and R&D approval. This method of monitoring has become standard in studies of medication where adherence is critical [27,28]. Sensors in the pill bottle tops detect opening and closing, and record these events with a date stamp. The sensors can be read at a later date, and therefore we can verify whether patients opened and closed their bottles at times that are consistent with their prescription. Oral medication dispensed to patients in MEMS bottles will be appropriately labelled according to the hospital pharmacy protocol. Oral antibiotic preparations which are not suitable for transfer from their original packaging will not be dispensed in MEMS bottles.

If more than one antibiotic is prescribed, we will use the MEMS sensors on the more frequently dosed antibiotic. If changes to antibiotic prescriptions are required after discharge, this may take place out-of-hours or at short notice in the community and therefore it may not be possible immediately to dispense replacements using MEMS.

The MEMS sensors will be collected and read at the next clinic visit after completion of the course in order to document how often the containers have been opened. The summary data on doses completed will then be entered in the eCRF by the local investigator.

23.8 5.7 Definition of End of Trial

The end of trial will be the day 365 visit follow-up of the last patient to be enrolled

23.9 5.8 Discontinuation/ Withdrawal of Participants from Study Treatment

Participants are eligible for entry to the study based on the available clinical information. If infection is not confirmed subsequently (see inclusion criteria above), or if the randomly allocated oral or IV strategy is subsequently judged to be clinically inappropriate and therefore cannot be completed, then the study participant will continue follow up in the trial. They will be included in the "intention to treat" analysis, but will not be included in "according to protocol" analysis. Routine clinical care consistent with the new information will be recommended.

Each participant has the right to withdraw from the study at any time. If a participant withdraws from the study during the randomized treatment phase, they will be offered routine clinical care. They will still be included in intention to treat analysis.

During the randomized treatment phase the investigator may discontinue a participant from the randomized therapy if it is not compatible with good clinical care. Details are given below under PO antibiotic strategy and IV

antibiotic strategy. Follow up will continue. Discontinuation from follow up will only occur if the participant requests it. The data obtained to date will then be analysed as "intention to treat" but not "according to protocol". The reason for discontinuation of treatment will be recorded in the CRF.

23.105.9 Source Data

The eCRF reviews will be completed directly by the study clinician reviewing the patient (by web-based electronic data entry), and not transcribed later.

The eCRF will specify whether the data entry is based on review of the patient records made by another clinician, by telephone contact, or by direct observation.

The eCRF will be stored separately from the patient record, but the investigators will ensure all clinically relevant information is in the patient record. If, for any reason (including endpoint committee reviews), copies of patient records are needed for review outside of the patient's clinical care team, then personal identifying information will be covered on photocopying and the photocopies labelled with the participant number.

24 TREATMENT OF TRIAL PARTICIPANTS

24.1 6.1 Description of Study Treatment: PO vs IV antibiotic strategy

To be enrolled in the study, the patient must have completed 7 days or less of intravenous antibiotic therapy after appropriate surgery (i.e. not including pre-operative antibiotics), or, if no surgery is undertaken, the patient must have completed 7 days or less of intravenous antibiotic therapy after the start of treatment for the clinical episode in question.

Following randomization, 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).

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.

24.2 6.2 Storage of Study Treatment

The antibiotics are all routinely available in the hospital pharmacies, and will be stored in the usual way.

24.3 6.3 Compliance with Study Treatment

Compliance will be documented by patient questionnaire, using questions on numbers of doses missed during a week and during the last 24 hours.

24.4 6.4 Accountability of the Study Treatment

Not applicable.

24.5 6.5 Concomitant Medication

Only antibiotic prescribing will be recorded. Additional PO antibiotics for other indications or as adjunctive treatment (e.g. the addition of oral rifampicin to IV antibiotics) will be allowed in both groups.

24.6 6.6 Post-trial treatment

Participants will continue with normal care. No particular arrangements will be required as a consequence of participating in the study.

25 SAFETY REPORTING

The MHRA Clinical Trial Helpline has advised that the trial is not a Clinical Trial of an Investigational Medical Product as defined by the EU Directive 2001/20/EC and therefore no MHRA approval is required. The safety reporting section here therefore refers to our own procedures for recording adverse events and limited expedited reporting to the sponsor.

25.1 7.1 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence (i.e. not necessarily linked to medication, randomized or otherwise) that:

- Results in death OR
- Is life threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) OR
- Requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation. Planned admissions to hospital, for instance for elective surgery, are not considered SAEs OR
- Results in persistent or significant disability/incapacity OR
- Is a congenital anomaly/birth defect OR
- Other important medical events. Other events may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above.

Episodes of potential treatment failure which are forwarded to the endpoint committee for review will not be considered SAEs.

25.2 7.2 Procedures for SAEs

We will record all SAEs identified during the first year after randomisation. Data will include a description, dates of onset and resolution, severity, assessment of relatedness to randomized antibiotic strategy, whether the SAE is expected or unexpected, and other suspect drugs or devices and action taken.

25.3 7.3 Procedures for the reporting of SAEs to local R&D and REC

We will not undertake expedited reporting of SAEs (see below for definitions), since the antibiotics to be used in the trial are all licensed agents with well described safety profiles. All SAEs will be recorded in the CRF as described above.

Expected SAEs are defined as follows;

6) Complications of bone/joint surgery.
7) Complications of the bone or joint infection that the patient is undergoing treatment for (including potential endpoints).
8) Drug reactions already detailed in the product literature (i.e. the SMPCs and/or British National Formulary).
9) Drug reactions already detailed in the product literature (i.e. the SMPCs and/or British National Formulary) for concurrent medications given for routine clinical care.
10) Inter-current illness causally related to comorbid conditions that the investigator believes are likely diagnoses given the patient's history, age and other factors.

The investigator will use their judgement, such that SAEs technically meeting definitions above, but that seem unexpected in terms of severity, duration or other factors may be regarded as unexpected.

If an investigator becomes aware of an unexpected SAE during the trial, then they will report this to the CI or delegate (i.e. the trial physician) within 1 working day using fax number 01865 227671. In addition, they will make telephone contact with the CI or their delegate to alert them to the report. The CI (or their delegate) will discuss the SAE with the investigator to clarify clinical details if required, and will then be responsible for reporting the unexpected SAE within a further working day to the OUH R&D Department.

25.4 7.4 Annual Safety Reports

We will be examining the non-inferiority of different routes of administration of widely used, licensed antibiotics to treat infection. A Clinical Trials Authorisation is not required; therefore, we will not write developmental safety update reports.

25.5 7.5 Safety Reporting to DMC and Research Ethics Committee

If, in the opinion of the CI or the Sponsor, an unexpected SAE may be relevant to participant safety, then a detailed report will be prepared including an assessment of causality and severity and forwarded to the DMC. The DMC will be asked to make a recommendation regarding the safety of the trial in the light of this report.

A report will also be submitted to the REC that gave a favourable opinion of the study. This report will be submitted within 15 days of the CI (or delegate) becoming aware of the event, and will use the NRES report of serious adverse event form as currently available on the NRES website.

26 STATISTICS

26.1 Power calculation

In the Oxford pilot, 10 participants experienced a primary endpoint among the first *197* randomizations. Based on an anticipated5% 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. As the final control group failure rate remains unknown, and to optimise the potential utility of subgroup analyses, the recruitment target will remain 1050.

26.1.1 Analysis of Safety

SAEs will be tabulated by treatment allocation.

26.1.2 Analysis of Efficacy

26.1.2.1 Primary Endpoint

Based on intention to treat, 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 90% confidence intervals around the absolute unadjusted difference (i.e. oral-intravenous) is less than 5%, then the criteria of non-inferiority will be met.

26.1.2.2 Secondary Endpoints

Secondary analyses will include (i) a per-protocol analysis based on all participants who have received at least 4 weeks of randomised therapy, and, if in the PO group, did not exceed the limits set for length of IV antibiotics (see above), and (ii) ITT and per-protocol analyses in the subgroup with "definitive" or "definitive" / "probable" infection at randomisation. These secondary analyses will focus on consistency of point estimates and 95% CI rather than formal comparison with the 5% non-inferiority margin. We will similarly compare the proportions of participants with secondary endpoints, or the distributions of continuous secondary outcomes (ranksum tests) as defined below. Sub-group analyses will use interaction tests to determine the consistency of treatment effects by type of infection and infecting pathogen. In some centres, randomization to oral antibiotics will result in an increased use of antibiotics with particular properties in penetrating biofilms, such as rifampicin. We will record treatment intentions for both intravenous and oral routes at baseline before randomization. Subgroup analysis will compare efficacy of intravenous versus oral antibiotics according to whether (or not) rifampicin was an antibiotic choice for intravenous and oral arms (4 subgroups). We will also conduct subgroup analyses according to the clinician's specific antibiotic intentions recorded prior to randomization, to assess whether bias exists in terms of specific patients not following their intended treatment plan after randomization.

A survival analysis will be performed to assess post-randomisation surveillance bias, which would present as a delay in time to meeting an endpoint in one randomised group. Other secondary analyses will include regression models (logistic (binary) or quantile (continuous)) to calculate estimates of treatment differences for the primary and secondary endpoints adjusted for age, comorbidity, infecting pathogen, and type of infection.

26.1.2.3 Adherence

We will describe adherence to oral medication using data from the questionnaires (full cohort) and the MEMS data in 3 centres, particularly considering the number of days on which all doses were missed, and dosing intervals in the latter.

26.1.3 Diagnostic sub-group definitions

The clinical diagnostic inclusion criterion means the trial will reflect real-world practice, and will facilitate timely entry to the study.

However, in analysis we will use histology, microbiology and clinical details to determine "definitive" evidence of infection, defined by; a) isolating bacteria from 2 or more samples of bone/spine/peri-prosthetic tissue, where the bacteria are similarly typed OR b) a pathogenic organism (e.g. *Staphylococcus aureus* but not *Staphylococcus epidermidis*) on a single, closed, biopsy of native bone or spine OR c) diagnostic histology on bone/peri-prosthetic tissue OR d) a draining sinus tract arising from bone/prosthesis or 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.

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:

g) Radiological or operative findings of periosteal changes suggesting chronic osteomyelitis OR
h) Radiological findings suggesting discitis/spinal infection OR
i) The development of a discharging wound after an orthopaedic procedure where prosthetic material has been implanted OR
j) The presence of deep pus close to but not adjacent to bone/prosthetic joint/orthopaedic device OR
k) The presence of peri-prosthetic necrotic bone OR

l) 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 f) above is met.

The endpoint review committee will be blinded to treatment allocation and subsequent outcome. Secondary analysis will evaluate non-inferiority for "definitive" or "definitive"/ "probable" infections only.

26.1.4 Health Economic Analysis

The health economic evaluation will comprise two parts. In the first part, a within trial analysis will be performed based on the resource use and Health Related Quality of Life (EQ5D) data collected in OVIVA. We will use the BNF for antibiotic costs (with a sensitivity analysis for hospital pharmacy discounts). We will include the costs associated with IV administration based on staffing requirements, equipment cost, clinic visits and transport costs for patient visits as observed in the trial. For unplanned inpatient stays and additional outpatient attendances other than those related to IV administration, we will use standard NHS reference costs.

We will calculate mean costs in each arm of the trial and differences in costs between the two arms, with 95% confidence intervals. The EQ-5D instrument will be used to estimate per-patient quality-adjusted life years (QALY) with adjustment for any differences between the groups in EQ5D at baseline. Non-parametric bootstrapping techniques will be employed to confirm the robustness of the statistical analysis of cost, QALY and cost-per-QALY. Uncertainty in cost-effectiveness will be represented on the cost-effectiveness plane and as confidence intervals for cost-effectiveness ratios, or as cost-effectiveness acceptability curves, as appropriate.

The second part of the analysis will be to extrapolate the observed results in OVIVA beyond the clinical trial, in order to explore the potential lifetime cost-effectiveness of a switch in antibiotic strategy. This extrapolation will be made in each diagnostic group, using estimates of long-term recurrence from the literature, and the observed recurrence rates observed within the period of the trial. We will also use the published longer-term costs associated with disability, in order to reflect the consequences of treatment failure that persist beyond the end of the trial. Taking these estimates together, we will extrapolate the costs beyond the period of observation within the year of follow up in the trial. This will necessarily involve a series of assumptions in applying estimates from the literature, and extensive sensitivity analyses will be examined in order to explore the robustness of the estimates.

27 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

28 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

We will conduct remote monitoring of data entered in real time. The chief investigator will ask local investigators to confirm unusual values, and will undertake monitoring visits if there are concerns regarding the integrity of data that cannot be resolved remotely.

28.1 10.1 Data Monitoring Committee

A data safety monitoring board will be formed. The DMC will be composed of 3 members; Neil French (chair, Professor of Infectious Disease, Liverpool University), Colette Smith (Research Statistician, Royal Free Campus, UCL.) and Martin Llewelyn (Brighton and Sussex University).

If, during the course of the trial, one of the DMC members withdraws, we will identify a replacement with a similar background. The DMC will review the analysis plan, and their approval will be required before it can be implemented. The DMC will receive reports regarding unexpected SAEs, and will review the final study report. The DMC will be empowered to advise stopping or suspending the trial.

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. The DMC will also, on the basis of this review, determine a requirement for a further interim review during the course of the trial.

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).

If the study is below 50% of the projected recruitment rate after 10 months then, after appropriate discussion with the TSC, the CI will ask the DMC to review endpoint data, to reconsider the projected power of the study given the frequency of endpoints identified, and to make a recommendation regarding stopping the trial on grounds of futility if appropriate.

The DMC will meet to discuss the analysis plan before the investigators conduct the final analysis. The investigators will participate in part of these meetings, but the DMC will complete the meeting without an investigator presence before coming to a final view. 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.

28.2 10.2 Trial Steering Committee

A trial steering committee will be formed. The trial steering committee will have independent co-chairpersons (Graham Cooke, Imperial college London, and John Paul, health protection agency). In addition, the TSC will have two public/ patient group representatives (Fraser Old, Nuffield Orthopaedic Centre Network and Jennifer Bostock, Healthcare-Associated Infection Service Users Research Forum) and the chief investigator. If a member of the TSC withdraws during the course of the trial, we will identify a replacement with a similar background.

The Trial Steering Committee will meet at the start of the trial, and then yearly to review recruitment rates, protocol amendments, any protocol deviations identified, and may make recommendations to the sponsor regarding running the trial.

29 ETHICS

All clinicians involved in the study have acknowledged a position of equipoise in relation to treatment for bone and joint infections; they accept that there is currently insufficient evidence to determine whether oral antibiotics are inferior to intravenous antibiotics in this context. This uncertainty will be conveyed to patients both verbally at study introduction and in writing via the patient information sheet.

29.1 11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

29.2 11.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

29.3 11.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) and host institutions R&D committees for written approval. Annual progress reports will be submitted to OUH R&D and to the appropriate REC.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

29.4 11.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by NHS number and study number on the electronic CRF. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so. Data may be used for further ethically approved studies of antibiotic treatment and may be shared with other researchers; this may include use of data outside the European Union where laws may not protect data privacy to the same extent as in the UK. To ensure confidentiality, none of the data stored or transferred electronically will contain personal identifiers.

30 DATA HANDLING AND RECORD KEEPING

All data entry at the sites will be electronic. The patients will return questionnaires, using the stamped addressed envelopes provided on randomisation. The results of endpoint committee reviews will be kept on paper, stored by the chief investigator or their delegate, and the results of these endpoints will be entered by the trial physician into a second database, held separately, for which access will be restricted to the trial physician, statistician, and DMC. This database of endpoints will only be merged with the main trial database (which includes treatment allocations) at the end of the trial, or at the request of the DMC. Investigators will not undertake any interim analyses using these data, either on a site-specific basis or for the whole trial.

31 FINANCE AND INSURANCE

The trial investigators are all NHS employees, covered by the standard NHS indemnity. The study will be sponsored by the OUH, and reviewed by the R&D department prior to starting, to ensure that appropriate indemnities are in place.

The running costs of the trial are funded by the NIHR HTA.

32 PUBLICATION POLICY

The outcome of the trial will be published in open access form. The DMC will review a manuscript before submission for publication, and authorship will be according to the ICJME criteria.

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16 APPENDIX A: EQ-5D QUESTIONNAIRE

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

Mobility

I have no problems in walking about □

I have some problems in walking about □

I am confined to bed □

Self-Care

I have no problems with self-care □

I have some problems washing or dressing myself □

I am unable to wash or dress myself □

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

I have no problems with performing my usual activities □

I have some problems with performing my usual activities □

I am unable to perform my usual activities □

Pain/Discomfort

I have no pain or discomfort □

I have moderate pain or discomfort □

I have extreme pain or discomfort □

Anxiety/Depression

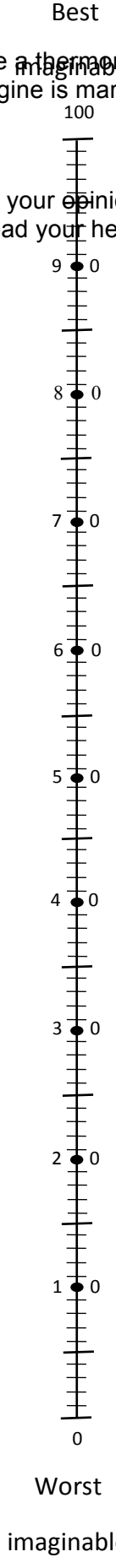
I am not anxious or depressed □

I am moderately anxious or depressed □

I am extremely anxious or depressed □

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line to whichever point on the scale indicates how good or bad your health state is today.



17 APPENDIX B: COMPLIANCE QUESTIONNAIRE

(Source: Morisky Adherence Measure Questionnaire)

You indicated that you are taking antibiotics medication for your bone or joint infection.

We are interested in your experience of taking your medication. There is no right or wrong answer. Please answer each question based on your personal experience.

1. Do you sometimes forget to take your antibiotics? YES NO

2. People sometimes miss taking their antibiotics for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your antibiotics?

YES NO

3. Have you ever cut back or stopped taking your antibiotics without telling your doctor, because you felt worse when you took it? YES NO

4. When you travel or leave home, do you sometimes forget about your antibiotics?

YES NO

5. Did you take your antibiotics yesterday? YES NO

6. When you feel like your infection is under control, do you sometimes stop taking your medicine?

YES NO

7. Taking antibiotics is a real inconvenience. Do you ever feel stressed about sticking to your antibiotic treatment plan? YES NO

8. How often do you have difficulty remembering to take all your medications? (Please circle the correct answer)

Never/Rarely Once in a while Sometimes Usually All the time

18 APPENDIX C (i): Oxford HIP SCORE QUESTIONNAIRE

1. During the past 4 weeks…

How would you describe the pain you usually have from your hip?

None	Very mild	Mild	Moderate	Severe

2. During the past 4 weeks…

Have you had any trouble with washing and drying yourself (all over) because of your hip?

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do

3. During the past 4 weeks…

Have you had any trouble getting in and out of a car or using public transport because of your hip? (whichever you tend to use)

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do

4. During the past 4 weeks…

Have you been able to put on a pair of socks, stockings or tights?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible

5. During the past 4 weeks…

Could you do the household shopping on your own?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible

6. During the past 4 weeks…

For how long have you been able to walk before pain from your hip becomes **severe**? (with or without a stick)

No pain/More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all/ pain severe on walking

7. During the past 4 weeks…

Have you been able to climb a flight of stairs?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible

8. During the past 4 weeks…

After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?

Not at all painful	Slightly painful	Moderately painful	Very painful	Unbearable

9. During the past 4 weeks…

Have you been limping when walking, because of your hip?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time

10. During the past 4 weeks…

Have you had any sudden, severe pain - 'shooting', 'stabbing' or 'spasms' - from the affected hip?

No days	Only 1 or 2 days	Some days	Most days	Every day

11. During the past 4 weeks…

How much has pain from your hip interfered with your usual work (including housework)?

Not at all	A little bit	Moderately	Greatly	Totally

12. During the past 4 weeks…

Have you been troubled by pain from your hip in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night

APPENDIX C (ii): OXFORD KNEE SCORE QUESTIONNAIRE

1. **During the past 4 weeks…**

   How would you describe the pain you usually have from your knee?

   None | Very mild | Mild | Moderate | Severe

2. **During the past 4 weeks…**

   Have you had any trouble with washing and drying yourself (all over) because of your knee?

   No trouble at all | Very little trouble | Moderate trouble | Extreme difficulty | Impossible to do

3. **During the past 4 weeks…**

   Have you had any trouble getting in and out of a car or using public transport because of your knee? (whichever you tend to use)

   No trouble at all | Very little trouble | Moderate trouble | Extreme difficulty | Impossible to do

4. For how long have you been able to walk before pain from your knee becomes **severe**? (with or without a stick)

   No pain/More than 30 minutes | 16 to 30 minutes | 5 to 15 minutes | Around the house only | Not at all/ pain severe on walking

5. **During the past 4 weeks…**

   After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

   Not at all painful | Slightly painful | Moderately painful | Very painful | Unbearable

6. **During the past 4 weeks…**

   Have you been limping when walking, because of your knee?

   Rarely/ never | Sometimes, or just at first | Often, not just at first | Most of the time | All of the time

7. **During the past 4 weeks…**

   Could you kneel down and get up again afterwards?

   Yes, easily | With little difficulty | With moderate difficulty | With extreme difficulty | No, impossible

8. **During the past 4 weeks…**

   Have you been troubled by pain from your knee in bed at night?

   No nights | Only 1 or 2 nights | Some nights | Most nights | Every night

9. **During the past 4 weeks…**

   How much has pain from your knee interfered with your usual work (including

housework)?

Not at all	A little bit	Moderately	Greatly	Totally

10. During the past 4 weeks…

Have you felt that your knee might suddenly 'give way' or let you down?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time

11. During the past 4 weeks…

Could you do the household shopping <u>on your own</u>?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible

12. During the past 4 weeks…

Could you walk down one flight of stairs?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible

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

Statistical Analysis Plan

Version 1.0 - 28/01/2015

Based on version 1.6 - 20/01/2014 of protocol

	Name	Title/Role	Signature	Date
Author	Ines Rombach	Trial Statistician		
Reviewer	Sarah Walker	Senior statistician		
Approver	Sue Dutton	Senior statistician		

Oxford Clinical Trials Research Unit (OCTRU)

and

RCS Surgical Intervention Trials Unit

Contents

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 (Oxford Clinical Trials Research Unit)

ines.rombach@ndorms.ox.ac.uk

Chief Investigator:

Matthew Scarborough (Oxford University Hospitals)

matthew.scarborough@ouh.nhs.uk

Trial Co-ordinator:

Rhea Zambellas (Oxford Clinical Trials Research Unit)

rhea.zambellas@ndorms.ox.ac.uk

Trial Physician:

Ho Kwong Li (Oxford University Hospitals)

Ho-Kwong.Li@ouh.nhs.uk

DSMC Members:

Neil French, DMC chair, Professor of Infectious Disease, Liverpool University, n.french@liverpool.ac.uk

Colette Smith, Lecturer in Biostatistics, UCL, c.smith@ucl.ac.uk

Martin Llewelyn, Reader in Infectious Diseases and Therapeutics, Brighton and Sussex University, M.J.Llewelyn@bsms.ac.uk

TSC Members:

Dr Graham Cooke, Consultant Infectious Disease and Senior Lecturer, g.cooke@imperial.ac.uk

Dr John Paul, Lead Public Health microbiologist, South East Region, John.Paul@bsuh.nhs.uk

Mr Fraser Old, retired, fraser@fracath.net

Ms Jennifer Bostock, Mental Health Act Commissioner for CQC, jennifer@jlbostock.plus.com

2. CHANGES FROM PREVIOUS VERSION OF SAP

This is the first version of the statistical analysis plan, based on protocol version 1.6, 30th September 2014

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;

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

27) Adherence, as indicated a) by questionnaire and b) 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/Mar/2012 March – start of main study
	03/06/2010 – start of internal pilot
Date of expected end of recruitment*:	31/10/2015
Date expected end follow-up*:	31/10/2016
Date expected analysis*:	01/11/16 – 20/01/17
Target number of subjects:	1050 (approximately 525 per arm) including the pilot

*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).

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

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.

The sample size calculations checked and the estimated sample size was deemed sufficient to meet the trial objective.

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 5% higher than the proportion of participants with definitive treatment failure in the IV group:

$p_{PO} - p_{IV} > 5\%$, 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 5% higher than the proportion of participants with definitive treatment failure in the IV group:

$p_{PO} - p_{IV} <= 5\%$, where p_{PO} and p_{IV} are the proportions of participants with definitive treatment failures randomised to the PO and IV strategies respectively

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.

17) 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
18) 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.
19) 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
20) 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 5% higher than the proportion of participants with any treatment failures in the IV group.

    $p_{PO} - p_{IV} > 5\%$, 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 5% higher than the proportion of participants with any treatment failure in the IV group.

    $p_{PO} - p_{IV} <= 5\%$, where p_{PO} and p_{IV} are the proportions of participants with any treatment failures randomised to the PO and IV strategies respectively

21) 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.

22) 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.
23) Quality of life evaluated by EQ-5D questionnaire
H_o: There is no difference in the median EQ-5D index between the two randomised trial arms
Median ($EQ\text{-}5D_{PO}$) = Median ($EQ\text{-}5D_{IV}$)
H_1: There is a difference in the median EQ-5D index between the two randomised trial arms
Median ($EQ\text{-}5D_{PO} \neq$ Median ($EQ\text{-}5D_{IV}$)
24) 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 ($OHS_{PO} \neq$ Median (OHS_{IV})
Median ($OKS_{PO} \neq$ Median (OKS_{IV})
25) Adherence to oral medication in terms of the MEMS caps and self-reported adherence.
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. Primary endpoints and secondary endpoint 3 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 by questionnaire in all centres, and in a subset (i.e. Oxford, Guy's and St Thomas' Trusts, Royal Free Hospital Trust and the Royal National Orthopaedic Hospital) using MEMS.

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 questionnaire
Day 0, 120, 365	Oxford Hip/Knee Questionnaire
Day 14, 42	Adherence 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, 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 review the analysis plan, and their approval will be required before it can be implemented. The DMC will receive reports regarding unexpected SAEs, and will review the final study report. The DMC will be empowered to advise stopping or suspending the trial.

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. The DMC will also, on the basis of this review, determine a requirement for a further interim review during the course of the trial.

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 meet to discuss the analysis plan before the investigators conduct the final analysis. The investigators will participate in part of these meetings, but the DMC will complete the meeting without an investigator presence before coming to a final view. 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.

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.

6. DESCRIPTIVE ANALYSES

6.1 Representativeness of Study Sample and Patient Throughput

A complete CONSORT flow 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 (and 95% Confidence intervals), 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 with absolute risk differences (95% confidence interval [CI]). 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 we consider giving a prolonged intravenous placebo treatment to be unethical. Open label studies are at risk of bias. We have therefore described objective criteria for meeting the primary endpoint, 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 committee will also 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 determine the endpoint blind to treatment allocation.

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.

The endpoint committee will only be required to review potential treatment failure. All other secondary endpoints including SAEs, line complications, early termination of treatment and data for resource allocation will be determined directly by the local study clinicians.

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.

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:

m) Radiological or operative findings of periosteal changes suggesting chronic osteomyelitis OR
n) Radiological findings suggesting discitis/spinal infection OR
o) The development of a discharging wound after an orthopaedic procedure where prosthetic material has been implanted OR
p) The presence of deep pus close to but not adjacent to bone/prosthetic joint/orthopaedic device OR
q) The presence of peri-prosthetic necrotic bone OR
r) 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 analysis:

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

Modified intention to treat analysis (MITT): All randomised participants with both baseline and at least one post-baseline assessment for patient reported outcomes; for all other outcomes all randomised participants with at least one post-baseline assessment. Participants will also be excluded from this analysis if relevant baseline covariates (where relevant) are not available. Analyses using the MITT population will only be performed if more than 5% of all randomised participants are excluded from it.

Per protocol (PP): all participants who have received at least four weeks of their randomised therapy, 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). These participants are defined as not having exited early from their allocated strategy.

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, has been reached if any of the reports of potential treatment failures as recorded by the local clinical team have been 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.

In this analysis, any participant with incomplete follow-up and no event observed to date will be classed as not having experienced an endpoint. Death without clinical failure is not classed as a treatment failure for this analysis.

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 intervals (CIs) around the absolute unadjusted difference (i.e. oral-intravenous) is less than 5%, then the criteria of non-inferiority will be met.

For the interim analysis only:

The trial team appreciate that, for the interim analysis only, this analysis approach may underestimate the event rate by including participants who have not completed their follow-up and may therefore yet experience a potential treatment failure. Therefore, these calculations will be repeated on the subset of participants who have been randomised at least 12 months from the cut-off date for data inclusion for the interim analysis (i.e. have completed their follow-up), and on a subset of the participants who have completed data for the day 42 assessment, or have been in the trial for at least 49 days (i.e. 42 days plus 7 days for data entry). This assessment is the first formal opportunity to notify the trial team of potential treatment failures. All three analyses will be referred to when assessing the appropriateness of the assumptions made in the sample size calculation in the interim analysis.

In addition, the above calculations will be repeated separately for participants from Oxford vs. participants from all other sites, to assess potential differences in failure rates which may be taken into account when assessing the appropriateness of estimates used in the sample size calculation.

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 5% non-inferiority margin. Details of these analyses are given below, or in the subgroup analyses section:

An initial supporting analysis will include a repetition of the above described analysis using the MITT (if appropriate) and PP populations.

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 infection pathogen and type of infection can be found in sections 8.5.3 and 8.5.2 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.
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 an endpoint in one randomised group, as well as loss to follow-up or death without and event, a survival 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 follow-up, 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 survival 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.

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.

The primary analysis makes the assumption that all participants with missing data will not have experienced any treatment failures during this time, based on the argument provided above.

Low percentages of missing data are not expected to have a significant impact on the trial results, and therefore no sensitivity analysis to examine the impact of missing data is planned if complete outcome data is available for more than 90% of participants (i.e. less than 10% of participants are lost or withdraw from follow-up before one year).

However, in the event that the extent of missing data will exceed this level, multiple imputation models will be used to adjust for missing data. Data will be imputed based on the covariates used in the multivariable models (allowing for a possible non-linear effect of age), the log(last follow-up time) and a treatment failure indicator which will be set to missing for those with incomplete follow-up due to loss/withdrawal. 20 imputed datasets will be created, and results will be pooled using the standard methodology (Rubin's rule) and commands in Stata (mi estimate). Visual checks to compare the distribution of observed and imputed values will be performed to ensure the imputation model includes non-linear effects of continuous variables where appropriate. Multiple imputation assumes that the missing data follows a missing at random mechanism, i.e. the probability of an observation being missing can be explained by the observed data. Under this assumption, an imputation model that includes the appropriate variables will produce unbiased results.

A secondary sensitivity analysis to assess the potential impact of missing data will also include a data NMAR scenario, assuming that participants with missing data have worse outcomes than those with complete follow-up data, following the approach by White et al[1].

8.5 Pre-specified Subgroup Analysis

All subgroup analyses will be 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.

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 u 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) 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 for all participants and the OKS/ OHS in the relevant subset of participants, adherence to the allocated intervention and cost-effectiveness.

More details on the secondary endpoints are provided in section 92.

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, OKS and OHS) and the patient reported adherence (Morisky Medication Adherence Scale) are scored in accordance to their respective scoring manuals. Information on all relevant scoring manuals are included in the appendix.
  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.

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 ITT 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 analysis described in section 8.2 will be repeated.

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 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 on early termination for good clinical response separately from other reasons (vs completion as planned).

9.2.5 Quality of life evaluated by the EQ-5D 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 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

Self-completed adherence with the allocated strategy as collected by the Morisky Adherence Measure Questionnaire will be presented for all participants randomised to the oral antibiotics and those who are self-administering the IV antibiotics is a secondary endpoint of this study and will be reported in the appropriate section of this report.

To create a better understanding of the adherence with the self-administered medication, percentage of adherent and non-adherent patients are displayed for each of the eight questions, as well as descriptive statistics (median, interquartile range and range) for the adherence score.

In addition, 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, which can be compared to the results of the self-reported medication adherence.

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.

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.

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 weeks), and the specific long-term regimens, will also be summarised overall and by treatment arm.

Time to permanent discontinuation of all antibiotic treatment (defined as the first day where antibiotics are not taken for the next 30 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

No additional exploratory analysis is 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.

12. APPENDIX:

12.1 Glossary of abbreviations

CI	Chief Investigator
DMC	Data Monitoring Committee
IV	Intravenous antibiotics
PO	Per Oral antibiotics
SAP	Statistical Analysis Plan
TSC	Trial Steering Committee

12.2 EQ-5D 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[2].

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)[3] can be referred to for additional detail.

12.4 Morisky Medication Adherence Scale scoring details

All eight questions to the Morisky Medication Adherence Scale are scored either zero for compliance with the medication, or one for non-compliance (see Figure 1 below).

A total score for the Morisky Medication Adherence Scale is derived by adding up the scores for all questions.

Morisky 8-Item Medication Adherence Questionnaire

Question	Patient Answer (Yes/No)	Score Y=1; N=0
Do you sometimes forget to take your medicine?		
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?		
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
When you travel or leave home, do you sometimes forget to bring along your medicine?		
Did you take all your medicines yesterday?		
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
How often do you have difficulty remembering to take all your medicine? __ A. Never/rarely __ B. Once in a while __ C. Sometimes __ D. Usually __ E. All the time		A = 0; B-E = 1
	Total score	

Scores: >2 = low adherence
1 or 2 = medium adherence
0 = high adherence

Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986;24:67-74.

Figure 1: Morisky Medication Adherence Scale - scoring instructions

13. DOCUMENT HISTORY

Add a brief document history – this can be removed when each full version is formally signed off, but all previous versions should be stored as a record of reviews of the document.

Version number Issue date	Author	Significant changes from previous version
V1.0_DDMonYYYY	Ines Rombach	Not applicable as this is the 1st issue
		Add to or delete as required

14. REFERENCES

1. White IR, Carpenter J, Horton NJ. Including all individuals is not enough: lessons for intention-to-treat analysis. *Clinical trials* 2012; **9**(4): 396-407.
2. Oemar M, Oppe M. EQ-5D-3L User Guide - Basic information on how to use the EQ-5D-3L instrument, Version 5.0. 2013 (accessed 1st October 2014).
3. Murray DW, Fitzpatrick R, Rogers K, et al. The use of the Oxford hip and knee scores. *The Journal of bone and joint surgery British volume* 2007; **89**(8): 1010-4.

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


SITU
SURGICAL INTERVENTION TRIALS UNIT

Contents

15. 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.

15.1 Key personnel

Trial statistician(s):

Ines Rombach (Surgical Intervention Trials Unit)

ines.rombach@ndorms.ox.ac.uk

Chief Investigator:

Matthew Scarborough (Oxford University Hospitals)

matthew.scarborough@ouh.nhs.uk

Trial Manager:

Rhea Zambellas (Surgical Intervention Trials Unit)

rhea.zambellas@ndorms.ox.ac.uk

Trial Physician:

Ho Kwong Li (Oxford University Hospitals)

Ho-Kwong.Li@ouh.nhs.uk

DSMC Members:

Neil French, DMC chair, Professor of Infectious Disease, Liverpool University, n.french@liverpool.ac.uk

Colette Smith, Lecturer in Biostatistics, UCL, c.smith@ucl.ac.uk

Martin Llewelyn, Reader in Infectious Diseases and Therapeutics, Brighton and Sussex University, M.J.Llewelyn@bsms.ac.uk

TSC Members:

Dr Graham Cooke, Consultant Infectious Disease and Senior Lecturer, g.cooke@imperial.ac.uk

Dr John Paul, Lead Public Health microbiologist, South East Region, John.Paul@bsuh.nhs.uk

Mr Fraser Old, retired, fraser@fracath.net

Ms Jennifer Bostock, Mental Health Act Commissioner for CQC, jennifer@jlbostock.plus.com

16. 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.

17. BACKGROUND INFORMATION

17.1 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;

28) SAEs, including death (i.e. all cause) according to treatment allocation.
29) line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line).
30) *Clostridium difficile* associated diarrhoea

31) “probable” and “possible” treatment failure as composites with definitive treatment failure (see endpoint definitions and analysis section for details).
32) early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason.
33) resource allocation using; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs.
34) Quality of life, as evaluated by EQ-5D-3L questionnaire
35) Oxford Hip and Knee Scores (where infection is in the hip or knee)
36) Adherence, as indicated a) by questionnaire and b) by MEMS (see below) in a subset of participants.

17.2 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

*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

17.3 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.

17.4 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).

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.

17.5 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.

17.6 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.

17.7 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.

17.8 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

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.

26) 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
27) 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.
28) 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
29) 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

30) 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.
31) 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.
32) 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 $_{IV}$)
33) 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})
34) Adherence to oral medication in terms of the MEMS caps and self-reported adherence.
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 by questionnaire in all centres, and in a subset (i.e. Oxford, Guy's and St Thomas' Trusts, Royal Free Hospital Trust and the Royal National Orthopaedic Hospital) using MEMS.

17.9 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 2: 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
Day 14, 42	Adherence Questionnaire

17.10 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).

18. 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.

19. 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.

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

20. DESCRIPTIVE ANALYSES

20.1 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.

20.2 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.

20.3 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.

20.4 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).

20.5 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.

20.6 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.

20.7 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:

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:

s) Radiological or operative findings of periosteal changes suggesting chronic osteomyelitis OR
t) Radiological findings suggesting discitis/spinal infection OR
u) The development of a discharging wound after an orthopaedic procedure where prosthetic material has been implanted OR
v) The presence of deep pus close to but not adjacent to bone/prosthetic joint/orthopaedic device OR
w) The presence of peri-prosthetic necrotic bone OR
x) 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.

21. 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.

22. 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).

22.1 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.

22.2 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[1]. 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
  - 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[2,3].

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 8.5.3 and 8.5.2 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 survival 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 survival 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.

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.

22.3 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.

22.4 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[4-6], 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.

22.5 Pre-specified Subgroup Analysis

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

22.5.1 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.

22.5.2 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:

7. Chronic osteomyelitis debrided, no current implant or device OR
   Discitis/spinal osteomyelitis/ epidural abscess debrided
8. Chronic osteomyelitis as above, but not debrided OR
   Discitis/spinal osteomyelitis/ epidural abscess but not debrided
9. Implant or device present and retained (i.e. “DAIR”)
10. Removal of orthopaedic device for infection OR
    Prosthetic joint implant removed
11. Prosthetic joint implant, 1-stage revision
12. 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.

22.5.3 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:

7. Staph Aureus

8. Pseudomonas spp
9. Gram negative organism(s)
10. Streptococcus
11. Coagulase negative Staphylococcus
12. 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.

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.

22.5.4 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.

22.6 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.

22.7 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.

23. 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 92.

23.1 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) and the patient reported adherence (Morisky Medication Adherence Scale) are scored in accordance to their respective scoring manuals. Information on all relevant scoring manuals are included in the appendix.

  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.

23.2 Statistical Methods Used for Analysis of Secondary Outcomes

23.2.1 "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.

23.2.2 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).

23.2.3 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.

23.2.4 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.

23.2.5 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.

23.2.6 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.

23.2.7 Adherence to oral medication

Self-completed adherence with the allocated strategy as collected by the Morisky Adherence Measure Questionnaire will be presented for all participants randomised to the oral antibiotics and those who are self-administering the IV antibiotics is a secondary endpoint of this study and will be reported in the appropriate section of this report.

To create a better understanding of the adherence with the self-administered medication, percentage of adherent and non-adherent patients are displayed for each of the eight questions, as well as descriptive statistics (median, interquartile range and range) for the adherence score.

In addition, 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, which can be compared to the results of the self-reported medication adherence.

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.

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

23.2.8 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

23.2.9 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.

23.2.10 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)

23.3 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.

24. ADDITIONAL ANALYSES

24.1 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.

24.2 Blinded analysis

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

24.3 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.

25. SAFETY ANALYSIS

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

26. APPENDIX:

26.1 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

26.2 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[7].

26.3 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)[8] can be referred to for additional detail.

26.4 Morisky Medication Adherence Scale scoring details

A modified Morisky Adherence scores are generated in line with the literature[9]. The score ranges from 0 to 8, with higher scores indicating better adherence. Scores of 8 indicate high adherence, 6-<8 indicates medium adherence of scores below 6 indicate low adherence.

27. 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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