**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)<br>Matthew.scarborough@ouh.nhs.uk<br>Tel 0787 2436461 |
| **Investigators:** | Philip Bejon (Oxford University Hospitals)<br>Guy Thwaites (Guys and St Thomas' Hospital London)<br>Hemant Pandit (Oxford University Hospitals)<br>Martin McNally (Nuffield Orthopaedic Centre)<br>David Beard (Oxford University, Trials Unit Director)<br>Cushla Cooper (Oxford University, Trial manager)<br>Andrew Seaton (Gartnavel General Hospital, site PI)<br>Andy Briggs (Glasgow University, Health economics analysis)<br>Rachel Midgley (Oncology Clinical Trials Office)<br>Carolyn Hemsley (Guys and St Thomas' Hospitals, site PI)<br>Jonathan Sandoe (Leeds Teaching Hospitals Trust, site PI)<br>Jonathon Folb (Royal Liverpool University Hospital, site PI)<br>Claire Mackintosh (NHS Lothian, site co-PI)<br>Becky Sutherland (NHS Lothian, site co-PI)<br>Susan Hopkins (Royal Free Hospital, site PI)<br>Damien Mack (Royal Free Hospital, site PI)<br>Simon Warren (Royal National Orthopaedic Hospital, site PI)<br>Martin Williams (Bristol Royal Infirmary, site PI)<br>Neil Jenkins (Birmingham Heartlands, site PI)<br>Gavin Barlow (Hull Royal Infirmary, site PI)<br>Uli Schwab (Newcastle Hospitals Trust, site PI)<br>Ila Aggarwal (Tayside University Hospitals Trust, site co-PI)<br>Elinor Moore (Cambridge University Hospitals, site PI)<br>Julia Greig (Royal Hallamshire Hospital, Sheffield, site PI)<br>Jon Campion (Northampton General Hospital)<br>Nick Nicolaou (Tunbridge Wells Hospital, Pembury, Kent)<br>Catherine Sargent (Brighton and Sussex Hospitals PI)<br>Mel Newport (Brighton and Sussex Hospitals, co PI)<br>Simon Ellis (Wansbeck Hospital, Northumbria)<br>Caroline Barker (Norfolk and Norwich Hospitals, site PI)<br>Bijayendra Singh (Medway Maritime Hospital, site PI)<br>Ian Dos Remedios (University Hospitals of North Midlands, site PI)<br>Neena Bodasing (University Hospitals of North Midlands, co PI)<br>Parvez Moondi (Queen Elizabeth Hospital, King's Lynn), PI)<br>Rashmi Sharma (Blackpool NHS Foundation Trust, site PI)<br>Sarah Meisner (Royal United Hospital Bath NHS Trust, site PI)<br>Jim Buckley (North West London Hospitals NHS Trust, site PI)<br>Michael Kelsey (Wittington Hospitals NHS Trust, site PI) |



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

| | |
|---|---|
| | Benjamin Lipsky (Endpoint committee chair)<br>Deepa Bose (Endpoint committee)<br>Harriet Hughes (Endpoint committee)<br>Ines Rombach (Oxford University, statistician)<br>Sarah Walker (Oxford University, senior statistician) |
| **Sponsor:** | Oxford University Hospitals NHS Trust |
| **Funder:** | NIHR HTA programme<br>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 (Print Name) | Investigator Signature | Date |
|---|---|---|

**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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

**TABLE OF CONTENTS**





© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

**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) |
| 2 | **1.3** | 11.01.13 | M Scarborough | Provision for signed assent in the event that a patient loses capacity during the trial. (5.5.2) |
| 3 | **1.3** | 11.01.13 | M Scarborough | Provision for potential data transfer outside the EU (5.5.2 and 11.4) |
| 4 | **1.3** | 11.01.13 | M Scarborough | Inclusion with the PIS, an invitation letter from clinicians responsible for participants |
| 5 | **1.4** | 01.07.2013 | M Scarborough | Amendment to the membership of the DMC and TSC to comply with recommendations of the HTA ( 10.1 and 10.2) |
| 6 | **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) |
| 7 | **1.5** | 20.01.14 | 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) |



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

| | | | | |
|---|---|---|---|---|
| 8 | **1.5** | 20.01.14 | M Scarborough | Inclusion of additional sites to the trial |
| 9 | **1.5** | 20.01.14 | M Scarborough | Facility for MEMS cap bottles to be prepared by ward pharmacists and trial staff (5.6.2) |
| 10 | **1.6** | 30.09.14 | M Scarborough | 12 months extension to recruitment |
| 11 | **1.6** | 30.09.14 | M Scarborough | Amendment of participating sites (5.3.1) |
| 12 | **1.6** | 30.09.14 | M Scarborough | Facility for MEMs monitoring at additional sites (5.6.2) |
| 13 | 2 | 01.05.15 | M Scarborough | Amendment of participating sites (5.3.1) |
| 14 | 2 | 01.05.15 | M Scarborough | Correction of typographical and copy errors |
| 15 | 2 | 01.05.15 | M Scarborough | Adjustment of non-inferiority margin (8.1) |
| 16 | 2 | 01.05.15 | M Scarborough | Addition of limited qualitative study to investigate barriers to recruitment (15, appendix D and bibliography) |
| 17 | 2 | 01.05.15 | M Scarborough | Present the Oxford Hip score and Oxford Knee score as separate appendices (18, appendix Ci and ii) |



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 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, 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** | 1. Serious adverse events, including death (all cause)<br>2. Line complications (i.e. infection, thrombosis or other events requiring early removal or replacement of the line).<br>3. *Clostridium difficile* associated diarrhoea<br>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.<br>5. Early termination of the planned 6 week period of oral or IV antibiotics because of adverse events, patient preference or any other reason.<br>6. resource allocation assessed using; a) length of inpatient hospital stay b) frequency of outpatient visits c) antibiotic prescribing costs.<br>7. Quality of life evaluated by EQ-5D questionnaire<br>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 |



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

| | |
|---|---|
| | surgery.<br>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 |
| 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 |



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

# 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,



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

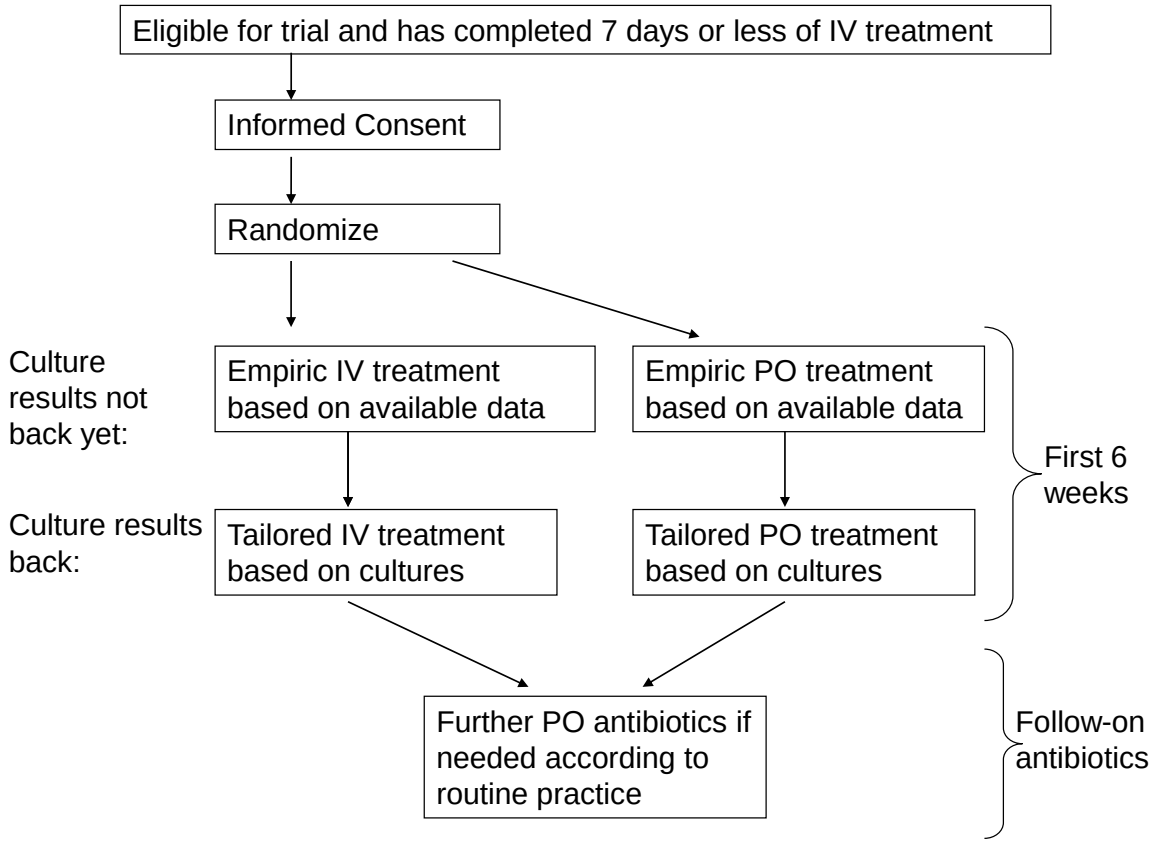
determined by usual clinical practice. Randomization group will not determine whether "follow on" antibiotics are given, or the length of the "follow on" treatment.

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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

### 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).



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

### 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, 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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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.

### 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

### 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 |



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

| | |
|---|---|
| | 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 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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.

### 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 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.

### 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 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.

### 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

### 5.6.2 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.

## 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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

### 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.

### 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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

90% confidence intervals around the absolute unadjusted difference (i.e. oral-intravenous) is less than 7.5%, 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 7.5% 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:



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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 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.

### 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 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), 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.

### 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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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.

## 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 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 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.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

# 15 QUALITATIVE RECRUITMENT INVESTIGATION

## 15a Rationale

Recruitment to the OVIVA trial has been unexpectedly difficult and, despite the instigation of multiple strategies to facilitate participation, the trial has had to request an extension. Factors contributing to the slower than expected accrual are multifactorial but are likely to include influence of both researchers and potential participants. We believe that a better understanding of barriers to participation will support the NIHRs objective in promoting engagement in research and optimising recruitment potential.

## 15b Background

The recruitment of patients into clinical trials presents a significant problem for researchers. Poor recruitment is a widespread problem [29]. Qualitative methods are increasingly being used to understand these issues since they provide an ideal approach for exploring the underlying motivations and reasons behind behaviour [30]. Some work has been done to understand recruiters' perspectives in randomised controlled trials, particularly in the identification of hidden agendas [31]. It has been suggested that increased support and incentives for patients can improve recruitment.

## 15c Aims and Objectives

The objective of this sub-study is to identify factors that impact on participation in the OVIVA trial, including the involvement of collaborators and patients. Understanding these issues will help us to better understand potential barriers to recruitment. It may also help us to develop strategies to improve recruitment in future clinical trials.

## 15d Methodology

10-20 semi-structured interviews will be conducted with patients and collaborators, using the Topic Guides (see Appendices G and H). Participants will be drawn from five study sites exhibiting a range of recruitment rates.

Sampling Strategy:

The sample will include up to 10 patients who either took part or declined to take part in the OVIVA trial and up to 10 collaborators who are on the delegation log for OVIVA recruitment.

Purposive sampling will be used to include participants with a range of characteristics and with varying levels of involvement in OVIVA.

Patient Recruitment

Patient participants will be recruited only from the Oxford site, single tertiary specialist orthopaedic hospital. This is a possible limitation with regards to analysing responses from clinical staff but it has the advantage of minimising differences in patients' experience of treatment pathways and the procedure used for screening and recruitment to the clinical trial. Given that the study focusses primarily on barriers to recruitment form a patient perspective, we believe that the advantages of single site recruitment outweigh the disadvantages. Expansion to multiple sites would not be possible without significant resource implications and would be likely to require a separate funding stream. If the results of this this preliminary study identify specific



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

barriers to recruitment which may be amenable to an intervention, a wider proposal will be considered.

Patients who have been approached to participate in OVIVA, will be asked to read the Qualitative Research Information Sheet For Patients. (see Appendix D). This information sheet will be offered to patients who have either agreed or declined to take part in the OVIVA trial. If they wish to take part, they will be asked to sign a specific Qualitative Research Consent Form (see Appendix F).

Collaborator Recruitment

Collaborators will be invited from five participating sites. Potential participants will be sent the Qualitative Research Information Sheet for Researchers (see Appendix E) and offered an opportunity to discuss the sub-study further with the Qualitative Researcher Lead. Those who wish to take part will be asked to sign the specific Qualitative Research Consent Form (see appendix F).

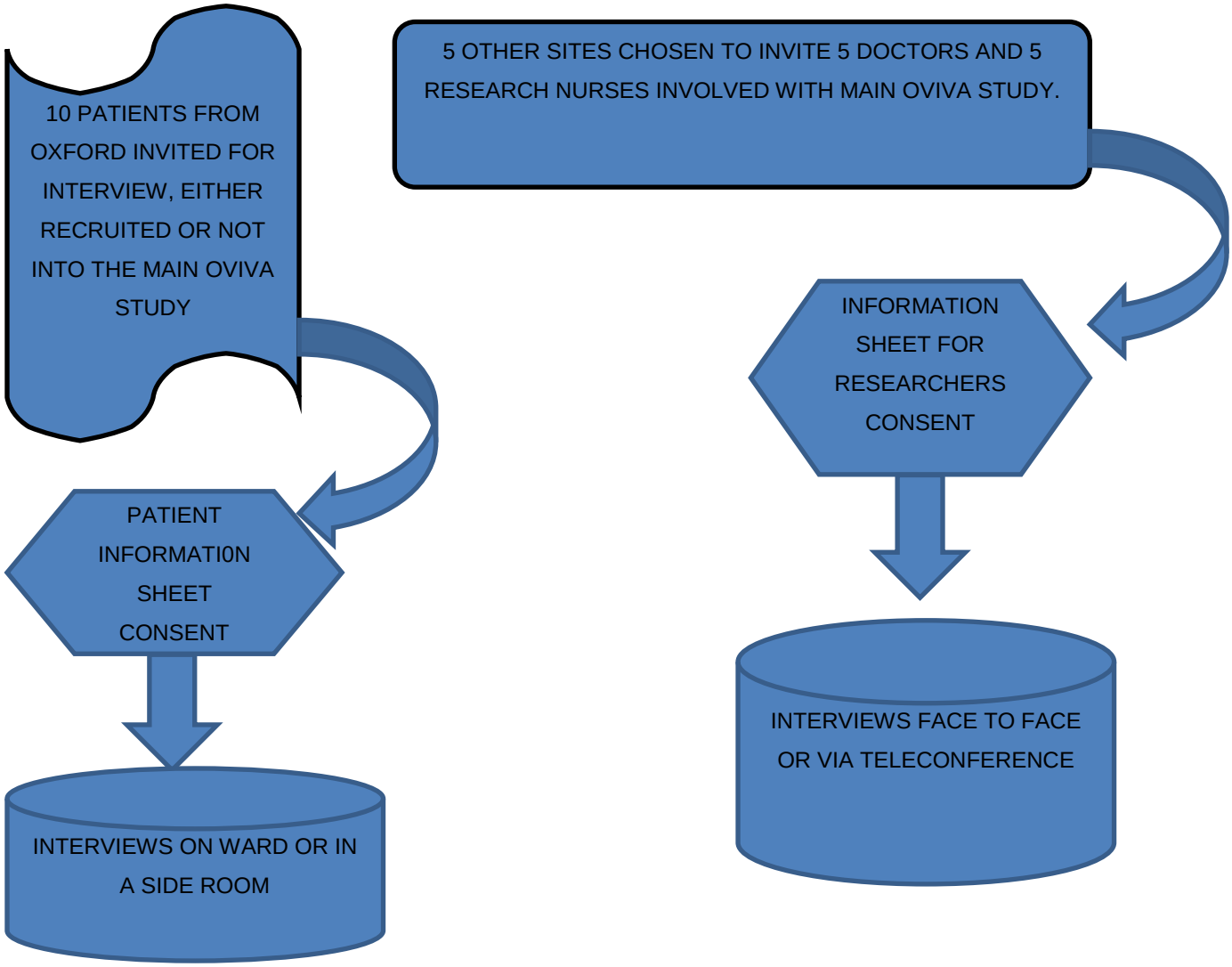
Data Collection

Interviews with Collaborators will be conducted either face to face or via teleconference. Two structured topic guides will be used for patients and collaborators to ensure similar questions are asked of all participants (see Appendices G and H). Questions will include experiences of the recruitment process and understanding of the study.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## Qualitative aspect of OVIVA




### 15e Analysis

Data will be audio-recorded, transcribed, anonymised and imported into the qualitative data programme NVivo. Thematic analysis will be used to identify common



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

and emergent themes in the interview data [32], until a satisfactory saturation level is found. Throughout the analysis the perspectives of the collaborators and patients will be compared and contrasted and data displayed on charts using the framework approach to data organisation [33]. Descriptive accounts of the data will then be generated.

**15f. Data Handling**

All information collected for the qualitative research aspect will be kept strictly confidential, with reference to the unique study number for OVIVA qualitative research, and all personal identifiers removed. Access to audio recordings and transcripts will be limited to qualitative researchers only, and will only be made available to the Qualitative Research Lead. Recorded data will be transferred and stored on University of Oxford password protected devices. Participants will not be identified in any way whatsoever, in any report or publication.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

REFERENCES

1. Lew DP, Waldvogel FA (2004) Osteomyelitis. Lancet 364: 369-379.
2. Zimmerli W, Ochsner PE (2003) Management of infection associated with prosthetic joints. Infection 31: 99-108.
3. Legrand E, Flipo RM, Guggenbuhl P, Masson C, Maillefert JF, et al. (2001) Management of nontuberculous infectious discitis. treatments used in 110 patients admitted to 12 teaching hospitals in France. Joint Bone Spine 68: 504-509.
4. Berman SJ, Johnson EW (2001) Out-patient parenteral antibiotic therapy (OPAT): clinical outcomes and adverse events. Hawaii Med J 60: 31-33.
5. Matthews PC, Conlon CP, Berendt AR, Kayley J, Jefferies L, et al. (2007) Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at home? A retrospective analysis of a large cohort over 13 years. J Antimicrob Chemother 60: 356-362.
6. Tice A (2001) Outpatient parenteral antimicrobial therapy (OPAT): a global perspective. Introduction. Chemotherapy 47 Suppl 1: 1-4.
7. Yong C, Fisher DA, Sklar GE, Li SC (2009) A cost analysis of Outpatient Parenteral Antibiotic Therapy (OPAT): an Asian perspective. Int J Antimicrob Agents 33: 46-51.
8. Tice AD, Marsh PK, Craven PC, McEniry DW (1993) Home intravenous antibiotic therapy. Am J Med 94: 114-115.
9. Tice AD (1993) Outpatient parenteral antibiotic therapy. Management of serious infections. Part II: Amenable infections and models for delivery. Osteomyelitis. Hosp Pract (Off Ed) 28 Suppl 2: 36-39; discussion 60-31.
10. Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JW, et al. (2006) Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ 333: 1193.
11. Montini G, Toffolo A, Zucchetta P, Dall'Amico R, Gobber D, et al. (2007) Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. BMJ 335: 386.
12. Shenep JL, Flynn PM, Baker DK, Hetherington SV, Hudson MM, et al. (2001) Oral cefixime is similar to continued intravenous antibiotics in the empirical treatment of febrile neutropenic children with cancer. Clin Infect Dis 32: 36-43.
13. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, et al. (2002) Linezolid versus vancomycin for the treatment of methicillin-resistant Staphylococcus aureus infections. Clin Infect Dis 34: 1481-1490.
14. Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, et al. (1996) Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med 101: 68-76.
15. Conterno LO, da Silva Filho CR (2009) Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev: CD004439.
16. Euba G, Murillo O, Fernandez-Sabe N, Mascaro J, Cabo J, et al. (2009) Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. Antimicrob Agents Chemother 53: 2672-2676.
17. Nguyen S, Pasquet A, Legout L, Beltrand E, Dubreuil L, et al. (2009) Efficacy and tolerance of rifampicin-linezolid compared with rifampicin-cotrimoxazole combinations in prolonged oral therapy for bone and joint infections. Clin Microbiol Infect.
18. Daver NG, Shelburne SA, Atmar RL, Giordano TP, Stager CE, et al. (2007) Oral step-down therapy is comparable to intravenous therapy for Staphylococcus aureus osteomyelitis. J Infect 54: 539-544.
19. Whittaker JP, Warren RE, Jones RS, Gregson PA (2009) Is prolonged systemic antibiotic treatment essential in two-stage revision hip replacement for chronic Gram-positive infection? J Bone Joint Surg Br 91: 44-51.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

20. Hart WJ, Jones RS (2006) Two-stage revision of infected total knee replacements using articulating cement spacers and short-term antibiotic therapy. J Bone Joint Surg Br 88: 1011-1015.
21. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE (1998) Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 279: 1537-1541.
22. Schrenzel J, Harbarth S, Schockmel G, Genne D, Bregenzer T, et al. (2004) A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. Clin Infect Dis 39: 1285-1292.
23. Drancourt M, Stein A, Argenson JN, Roiron R, Groulier P, et al. (1997) Oral treatment of Staphylococcus spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. J Antimicrob Chemother 39: 235-240.
24. Ceroni D, Regusci M, Pazos JM, Saunders CT, Kaelin A (2003) Risks and complications of prolonged parenteral antibiotic treatment in children with acute osteoarticular infections. Acta Orthop Belg 69: 400-404.
25. Daurel C, Prunier AL, Chau F, Garry L, Leclercq R, et al. (2007) Role of hypermutability on bacterial fitness and emergence of resistance in experimental osteomyelitis due to Staphylococcus aureus. FEMS Immunol Med Microbiol 51: 344-349.
26. Howden BP, Grayson ML (2006) Dumb and dumber--the potential waste of a useful antistaphylococcal agent: emerging fusidic acid resistance in Staphylococcus aureus. Clin Infect Dis 42: 394-400.
27. Diaz E, Levine HB, Sullivan MC, Sernyak MJ, Hawkins KA, et al. (2001) Use of the Medication Event Monitoring System to estimate medication compliance in patients with schizophrenia. J Psychiatry Neurosci 26: 325-329.
28. Farley J, Hines S, Musk A, Ferrus S, Tepper V (2003) Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr 33: 211-218.
29. Fletcher B, Gheorghe A, Moore D, Wislon S, Damery S (2012) Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review.
30. de Sallis I, Tomlin Z, Toerien M, Donovan J (2008) Using Qualitative Research methods to improve recruitment to randomized controlled trials: The Quartet Study.
31. Donovan J, Paramasvian S, de Sallis I, Toerien M (2014) Clear obstacles and hidden challenges: understanding recruiter persepctives in six pragmatic tandomised contolled trials.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 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 □

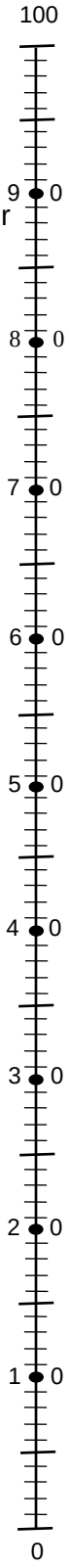


© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

Best imaginable health state

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.




Worst imaginable health state



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

# 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?



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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…**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

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



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

## 19 APPENDIX D: QUALITATIVE RECRUITMENT STUDY

# OVIVA Qualitative Research Interview (QRI)

# Information Sheet for Patients

**Audio-recordings and Interviews**

**The OVIVA Qualitative Recruitment Interview (QRI) has been set up to understand reasons for participation/non-participation into the OVIVA Study. This information sheet explains the purpose and conduct of the QRI to enable you to make an informed decision about participation. Please read the following information carefully and discuss with others if you wish. Please ask the qualitative researcher if you have any questions.**

### Aims

- **To understand why you decide to participate or decline to participate in the OVIVA Study**

### Methods

**You will be interviewed either on the ward or in a suitable room. This will take about 20 minutes of your time, and can be arranged when suitable to you.**

### What we hope to achieve

**We hope to understand how you feel about the study and about being asked to take part, as well as how we can improve the way we recruit. This will also help us for recruiting into future studies**

**Personal Participation:**
**Before agreeing to participate in the interview, you may want to consider the following questions:**

**1) Why am I being asked to participate?**

- **You are being invited to participate as you were eligible to take part in the OVIVA Study**

**2) What does participation involve?**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

- **Consent to participate in an audio-recorded interview about why you agreed or declined to participate in the OVIVA Study. . The interviewer will ask you to talk about your experiences of being approached to participate, and also ask some structured questions. The interview will be arranged while you are an in-patient and will last up to 20 minutes. All interviews will be audio-recorded for later transcription.**

**3) Do I have to take part?**

- **Participation in the interview is entirely voluntary.**

- **You can withdraw from the study at any time.**

- **You can refuse to answer questions during the interview.**

**4) Is my participation confidential?**

- **All information collected about you during the interview will be kept strictly confidential.**

- **Access to audio-recordings and transcripts will be limited to researchers working on the QRI of the OVIVA Study.**

- **Recorded data will be transferred and stored by staff at the University of Oxford on password protected devices.**

- **Personal identifiers will be removed from all transcripts and audio files will be stored using study numbers (not your name).**

**You will not be identified in any way whatsoever, in any report or publication.**

**5) What are the possible advantages of taking part?**

- **Participation will provide you with an opportunity to reflect upon your involvement in OVIVA.**

- **You will have an opportunity to discuss any difficulties or concerns with taking part.**

- **The results will help us to improve recruitment into the OVIVA Study, and other similar studies in the future.**

**6) What are the possible disadvantages of taking part?**

- **Giving up some of your time may be an inconvenience but please be reassured that the interview will take place at a time convenient to you.**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

- **You may feel that your decision to participate in OVIVA is being scrutinised, but we need to understand how we can improve recruitment, and your views and opinions are important to us. The clinicians caring for you and the OVIVA study clinicians will not be involved in the interviews.**

**7) Who is organising and funding the research?**
**The Qualitative Research Interviews and analysis are part of the OVIVA Study, which is funded by the National Institute of Health Research. (NIHR)**

**8) What if I have other concerns?**

**If you want to discuss the qualitative recruitment investigation, please contact:-**
**OVIVA Qualitative Research Lead**
**Rhea Zambellas**
**The Botnar Research Centre**
**University of Oxford**
**OX3 7LD**
**01865 223487**
**Rhea.zambellas@ndorms.oc.ac.uk**

**Should you wish to complaint about any aspect of the study, please contact either the principal investigator (PI) or the Patient Advice and liaison service on the numbers provided below..**

**PI: 07872436461**
**PALS: 01865 738126**

**Many thanks for reading this information sheet.**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

# OVIVA Qualitative Research Interview (QRI)

# Information Sheet for Researcher

**Audio-recordings and Interviews**

**The OVIVA Qualitative Recruitment Interview (QRI) has been set up to understand reasons for participation/non-participation into the OVIVA Study; researchers' and patients' perspectives. This information sheet explains the purpose and conduct of the QRI to enable you to make an informed decision about participation. Please read the following information carefully and discuss with others if you wish. Please ask the qualitative researcher if you have any questions.**

## QRI Aims

- **To understand why Researchers approach/do not approach patients to participate in the OVIVA Study in different centres.**
-

## QRI Methods

- **Recording and analysis of semi-structured interviews with OVIVA collaborators.**

## Anticipated Outcomes of the QRI

- **Strategies to improve recruitment to OVIVA, and maybe future studies.**
- **Publication of QRI findings in leading peer reviewed journals, as part of the OVIVA Study.**

## Personal Participation:

**Before agreeing to participate in the QRI, you may want to consider the following questions:**

**1) Why am I being asked to participate?**

- **You are involved in recruiting patients into the OVIVA Study (Doctor or Research Nurse)**

**2) What does participation in the QRI involve?**

- **Consent to participate in an audio-recorded interview about OVIVA. The interviewer will ask you to talk about your experiences of recruitment into OVIVA, and also ask some structured questions. The interview will be arranged at a time and place convenient to you and will last up to 30 minutes. All interviews will be audio-recorded and transcribed. For some sites, a teleconference will be arranged, again with audio-recording.**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

**3) Do I have to take part?**

- **Participation in the QRI is entirely voluntary.**
- **If you decide to take part, keep a personal signed copy of this information sheet and give a signed copy to the researcher.**
- **You can withdraw from the study at any time.**
- **You can refuse to answer questions during the interview.**

**4) Is my participation confidential?**

- **All information collected about you during the research will be kept strictly confidential.**
- **Access to audio-recordings and transcripts will be limited to researchers working on the QRI of the OVIVA Study.**
- **Recorded data will be transferred and stored by staff at the University of Oxford on password protected devices.**
- **Personal identifiers will be removed from all transcripts and audio files will be stored using study numbers (not your name).**
- **You will not be identified in any way whatsoever, in any report or publication.**

**5) What are the possible advantages of taking part?**

- **Participation will provide you with an opportunity to reflect upon your involvement in OVIVA.**
- **You will have an opportunity to discuss any difficulties or concerns with recruitment**
- 
- **The results will help us to improve recruitment into the OVIVA Study, and other similar studies in the future.**

**6) What are the possible disadvantages of taking part?**

- **You may feel that your recruitment strategy (Doctors and Research Nurses),is being scrutinised, but we need to understand how we can improve recruitment, and all your views and opinions are kept confidential.**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

- **If you want to complain about any aspect of the study or your involvement in it, the normal National Health Service complaints mechanisms should be available to you.**

**7) Who is organising and funding the research?**

**The Qualitative Research Interviews and analysis are part of the OVIVA Study, which is funded by the National Institute of Health Research. (NIHR)**

**8) What if I have other concerns?**

**If you want to discuss the qualitative recruitment investigation, please contact:-**
**OVIVA Qualitative Research Lead**
**Rhea Zambellas**
**The Botnar Research Centre**
**University of Oxford**
**OX3 7LD**
**01865 223487**
**Rhea.zambellas@ndorms.ox.ac.uk**

**Should you wish to complaint about any aspect of the study, please contact either the principal investigator (PI) or the Patient Advice and liaison service on the numbers provided below..**

**PI: 07872436461**
**PALS: 01865 738126**

**Many thanks for reading this information sheet.**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

# OVIVA Qualitative Research Investigation

# Consent Form

**Audio-recording of Consultations and Interview Contact**

**Please initial box**

1) I confirm that I have read and understood the Participant Information Sheet (v1, dated 13/8/14), and have had the opportunity to ask questions about the Interview. ☐
2) I understand that my participation is voluntary and I am free to withdraw at any time without given a reason. ☐
3) I agree to my contact details being sent to a researcher at the University of Oxford so I can be contacted to arrange an interview ☐
4) I agree to the use of the audio-recording of my interview for research and the interviewer taking notes. ☐
5) I agree to the study publishing anonymous quotations from the interviews ☐
6) I understand that data collected during the interview may be looked at by authorised researchers at the University of Oxford. ☐

Any information you give us will be kept strictly confidential.

Please sign below if you agree to take part in this research study:

Signed (patient): …… Date: …… (dd/mon/yyyy)

Name in block letters: ……...

Signed (recruiter): …… Date: ……..

Name in block letters……..

2 copies: Original to be filed in patient file – fax a copy to the OVIVA Study Co-ordinator 01865 572398 FAO Rhea Zambellas
Please provide the patient with a photocopy of the original form.



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

**STRUCTURAL FRAMEWORK FOR INTERVIEWS**

**Introduction**

- **Introduce self**
- **Introduce qualitative aspect of OVIVA**
- **Key points**
  - **Length of interview**
  - **Voluntary participation and right to withdraw**
  - **Recording of the interview**
- **Confidentiality**
- **Information Sheet they have already received – any questions from that**
- **Consent Form (sign together and give them a copy)**

**Interview with Patient**

**Section 1: Background information**

**Have you been recruited into the main OVIVA Trial?**

**Section 2: Ask them to describe their experience of the OVIVA recruitment process**

i. **Follow up questions – good/ bad/ why?**

**Section 3: Understanding of the OVIVA Study**

i. **Who explained the study**
ii. **Understanding of why the study is being done**
iii. **Feelings about receiving either treatment arm**

**Section 4: What has impacted on your decision about whether or not to take part?**

i. **Prompt: Any issues with privacy to talk on the open ward**
ii. **Any other factors contributing taking part or declining**

❖ **Conclusion: anything to add, thank them for time**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010

**Interview with the doctor or nurse:**

**Section 1: Background**

Background information: profession, how long they have been working with OVIVA study, their role in it.

**Section 2: Experiences of recruitment process**

- **Ask them first to describe their experience of the OVIVA recruitment process**
- **Have they recruited?**

**Section 3. What things impacted on whether they decided to recruit/ not to recruit patients?**

i. **Experience of the site initiation visit**
ii. **Issues with eligibility criteria**
iii. **Constraints in workload preventing recruitment**
iv. **Rapport with colleague**
v. **Prompt sheet useful or not?**
vi. **Avoidance of recruiting for personal reasons – views on treatment arms**
vii. **Understanding of R&D approval process/any concerns**

- *Experiences of site initiation visit - things that worked well/ not so well/ suggestions for improvement*
- *Views on eligibility criteria – was this clear/ anything not so clear/ improvements*
- *Views on prompt sheet – things that were helpful/ not so helpful/ improvements*
- *R&D approval process - clear or not so clear/ improvements*

❖ **Conclusion: Anything to add, thank them for time**



© Copyright: OUH NHS Trust 2010; adapted from The University of Oxford 2010