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A randomized clinical trial of low dose single antibiotic-loaded cement versus high dose dual antibiotic-loaded cement in patients receiving a hip hemiarthroplasty after fracture: A protocol for the WHiTE 8 COPAL study

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Aims

Patients receiving cemented hemiarthroplasties after hip fracture have a significant risk of deep surgical site infection (SSI). Standard UK practice to minimize the risk of SSI includes the use of antibiotic-loaded bone cement with no consensus regarding type, dose, or antibiotic content of the cement. This is the protocol for a randomized clinical trial to investigate the clinical and cost-effectiveness of high dose dual antibiotic-loaded cement in comparison to low dose single antibiotic-loaded cement in patients 60 years and over receiving a cemented hemiarthroplasty for an intracapsular hip fracture.

Methods

The WHiTE 8 Copal Or Palacos Antibiotic Loaded bone cement trial (WHiTE 8 COPAL) is a multi-centre, multi-surgeon, parallel, two-arm, randomized clinical trial. The pragmatic study will be embedded in the World Hip Trauma Evaluation (WHiTE) (ISRCTN 63982700). Participants, including those that lack capacity, will be allocated on a 1:1 basis stratified by recruitment centre to either a low dose single antibiotic-loaded bone cement or a high dose dual antibiotic-loaded bone cement. The primary analysis will compare the differences in deep SSI rate as defined by the Centers for Disease Control and Prevention within 90 days of surgery via medical record review and patient self-reported questionnaires. Secondary outcomes include UK Core Outcome Set for hip fractures, complications, rate of antibiotic prescription, resistance patterns of deep SSI, and resource use (more specifically, cost-effectiveness) up to four months post-randomization. A minimum of 4,920 patients will be recruited to obtain 90% power to detect an absolute difference of 1.5% in the rate of deep SSI at 90 days for the expected 3% deep SSI rate in the control group.

Conclusion

The results of this trial will provide evidence regarding clinical and cost-effectiveness between low dose single and high dose dual antibiotic-loaded bone cement, which will inform policy and practice guidelines such as the National Institute for Health and Care Excellence guidance on management of hip fractures.

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Introduction

Fragility hip fractures present a significant global challenge to patients, clinicians, and healthcare systems. It is estimated that hip fractures account for 0.1% of the global burden of disease worldwide.¹ With a growing elderly

population, the number of hip fractures will steadily increase with projections indicating approximately 100,000 patients annually requiring surgery by 2033 in England.² The total annual direct medical costs associated with incident hip fractures was estimated to

be £1.1 billion in the UK, with acute hospitalization as the main cost driver.³

Current National Institute for Health and Care Excellence (NICE) guidance on hip fracture management recommends the use of a cemented prosthesis for displaced intracapsular fractures due to improved post-surgical pain relief and functional outcomes.^{4,5} However, there is no guidance as to which sort of bone cement to use.

The National Hip Fracture Database (NHFD) reported an unadjusted 30day crude mortality for all hip fractures of 6.1% while published literature reported a risk in the range of 10% to 40% in the first year, with much of this attributed to postoperative complications.⁶⁻⁸ The most catastrophic of the postoperative complications is deep surgical site infection (SSI) with rates reported in the literature as high as 7.3% and one-year mortality rate attributed to infected hip hemiarthroplasties of up to 50%.⁹⁻¹¹

Perioperative antibiotics are one proven means of reducing deep SSI in patients undergoing elective total hip arthroplasty (THA).¹²⁻¹⁴ Antibiotic prophylaxis against deep SSI is administered parenterally, via bone cement or a combination of both. The use of both parenteral antibiotics and antibiotic-loaded bone cement (ALBC) is standard practice in the UK for cemented hemiarthroplasty after hip fracture with no consensus regarding type, dose, or antibiotic content of the cement. The evidence for use of ALBC in hip fractures is limited but there is increasing non-randomized clinical evidence showing that the use of premixed high dose gentamicin and clindamycin bone cement may have a clinically important effect in reducing SSI by over 50% compared to low dose gentamicin only preparations.¹⁵⁻¹⁷ In vitro experiments support these findings by showing increased antibiotic elution from the addition of clindamycin to gentamicin ALBC and furthermore demonstrating bacterial biofilm formation inhibition for extended periods.¹⁸ The concern with widespread use of high dose dual ALBC is increased cost, and the risk of increased antibiotic resistant periprosthetic joint infections, although published data on the later appears reassuring.¹⁶ There is also a theoretical risk of systemic toxicity, though there is little to no compelling data supporting this concern.¹⁹

This is the protocol for a randomized clinical trial to investigate the clinical and cost effectiveness of high dose dual antibiotic-loaded cement in comparison to low dose single antibiotic-loaded cement in patients 60 years and over receiving a cemented hemiarthroplasty for an intracapsular hip fracture.

Aims

This trial aims to establish if a high dose, dual antibiotic regime results in fewer deep SSI compared to low dose single antibiotic cement in patients receiving cemented hemiarthroplasties for intracapsular hip fractures.

The primary objective is to quantify and draw inferences on the rate of 'deep surgical site infection' within

90 days of surgery in the low dose single and high dose dual groups.

The secondary objectives are to quantify and draw inferences on observed differences in: the UK core outcome set for hip fractures²⁰ (health-related quality of life, mobility status, residential status, and mortality); antibiotic prescription for hip wound issues within 90 days post-surgery; antibiotic resistance profiles within 90 days post-surgery; rate of complications other than deep SSI within 120 days of surgery; the resource use, costs, and comparative cost-effectiveness of a high dose dual antibiotic cement versus a low dose single antibiotic cement during the first 120 days after randomization using appropriate statistical and economic analytical methods.

Methods

Study design. This is a multicentre, multi-surgeon, parallel, two-arm, randomized clinical trial. The pragmatic study will be embedded in the World Hip Trauma Evaluation (WHiTE) comprehensive cohort (ISRCTN 63982700).^{21,22}

The trial is expected to take 30 months to recruit with a further six months planned for final follow-up. Trial management will be conducted by the Oxford Trauma and Emergency Care research team at the University of Oxford according to the standard operating procedures of the Oxford Clinical Trials Research Unit (OCTRU).

Hypothesis. The null hypothesis is that there will be no differences in deep SSI rates within 90 days post-surgery between patients receiving high dose dual antibiotic-loaded cement versus low dose single antibiotic-loaded cement during cemented hemiarthroplasties for intracapsular hip fractures.

Eligibility. Patients will be screened against the following criteria:

Inclusion criteria. All patients, both those with and without capacity, presenting with a displaced intracapsular fracture of the hip suitable for hemiarthroplasty will be included.

Exclusion criteria. Patients younger than 60 years of age; patients who are managed nonoperatively; patients who are treated with a total hip arthroplasty; patients who are allergic to gentamicin or clindamycin.

Consent. Patients with a hip fracture are a clinical priority for urgent operative intervention on the next available trauma operating list. All patients with a fracture of the hip are in pain and would have received opiate analgesia. It is therefore understandable that patients may find the initial period of their treatment in hospital confusing and disorientating. Similarly, patients' next of kin, carers, and friends may have difficulty in weighing the large amounts of information that they are given about the injury and treatment plan. In this emergency situation the focus is on obtaining consent for surgery

(where possible) and on informing the patient and any next of kin about immediate clinical care. It is often not possible for the patient or relative/carer (consultee) to review trial documentation, weigh the information, and communicate an informed decision regarding participation. The consent procedure for this trial will reflect that of the surgery, with the clinical team assessing capacity before taking consent for the surgical procedure, and this capacity assessment will then be used to guide the approach to research consent. An appropriate method, in line with the Mental Capacity Act²³ and approved by the National Research Ethics Committee, will be used to gain either prospective or retrospective consent from the patient or appropriate consultee by a Good Clinical Practice (GCP) trained, appropriately delegated member of the research team.

Randomization. Eligibility will be confirmed prior to surgery and eligible patients will be enrolled into the trial via an online randomization system. The allocation sequence will be generated by the trial statistician. Randomization will be on a 1:1 basis, stratified by trial centre to ensure any clustering effect related to centre will be equally distributed in the trial arms. When a patient enters the trial, sufficient non-identifiable details will be logged preoperatively, by the clinical team, on a secure, encrypted, web-based system, provided by OCTRU. Basic information including the patient initials, age, and eligibility checks will be entered. The patient will then receive a unique Trial ID that will be used on all trial documentation. Trial allocation will be recorded on the Baseline Case Report Form (CRF) and details about the intervention received will be noted in the patient's operation notes. Patient contact details will be entered into a secure online database, separate from CRF data.

Blinding. The treating surgical team will not be blinded to the treatment allocation. The patients and outcome assessment will, however, be blinded to the treatment allocation.

Post recruitment withdrawals. Throughout the study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives. Participants who decline further contact can withdraw wholly from the study. In this case, a withdrawal form will be completed, and data obtained up until the point of withdrawal will be included in the final analysis of the study.

Treatment pathway

Preoperative assessment. Diagnosis of a hip fracture will be confirmed by a plain radiograph, as per routine clinical care. Supplementary imaging will be at the discretion of the treating clinical team. Routine investigations,

anaesthetic assessment, antibiotic and venous thromboprophylaxis will be used as per local policy.

Anaesthetic technique. A regional or general anaesthesia technique will be used for every participant as per routine clinical care. Intraoperative analgesia may be achieved by combining a local anaesthetic nerve block using either nerve stimulator or ultrasound-guided technique, paracetamol infusion, and opiate analgesia as clinically indicated.

Perioperative intravenous antibiotics. All participants will receive perioperative prophylactic intravenous antibiotics in accordance with current protocols agreed at each centre.

Trial intervention. Participants will be randomly allocated to one of two groups:

Group 1: Low dose single antibiotic bone cement; Heraeus Palacos R + G cement (Hanau, Germany) (contains gentamicin 0.5 gm per 40 gm mix of cement)

Group 2: High dose dual antibiotic bone cement; Heraeus Copal G + C cement (Hanau, Germany) (contains gentamicin 1 g and clindamycin 1 g per 40 gm mix of cement).

Surgical technique. All participants will undergo cemented hip hemiarthroplasty. The surgical approach, choice of prosthesis, femoral canal preparation technique, cementation technique, and surgical closure will be left to the discretion of the operating surgeon as per their usual practice.

Postoperative rehabilitation. Postoperative analgesia will be prescribed intraoperatively and reviewed by the responsible clinical teams as appropriate. In the postoperative period, as per standard of care, all participants will undergo physiotherapy and occupational therapy assessment to create a rehabilitation plan. The aim of this plan will be for participants to mobilize through early, active, full weight-bearing. Participants will be discharged from the acute orthopaedic trauma ward at the earliest safe opportunity to the most appropriate discharge destination as determined by the multidisciplinary clinical team.

Follow-up. Follow-up data related to deep infection while the patient is an inpatient at the research site will be collected at discharge by site research staff on the baseline CRF.

The 120-day follow-up data will be completed either by the local research staff, if the patient is still in hospital, or centrally by a data clerk at the University of Oxford. Follow-up data will be collected on a patient questionnaire in a telephone interview or via post if it is not possible to contact the patient, personal consultee, or carer via telephone.

Where a participant entered the study under nominated consultee advice and no personal consultee can be identified, we will contact the last known carer for further follow-up. Carer contact details will be provided to the trial team on trial entry for this purpose. Where patient or

carers cannot be contacted, or where complications are reported by a patient or carer, further information with regards to symptoms/treatment for of those complications will be obtained from the patient's general practitioner (GP) and/or recruiting site.

Finally, for participants that the trial team are unable to contact, the site team will be contacted to check the medical notes for information regarding complications. If all these methods of contact and data collection fail, then we will class the participant as a non-responder or "lost to follow-up" for that timepoint.

Adverse events. Safety reporting for each participant will begin from the first point of administration of the intervention and will end when the participant has reached their follow-up timepoint, at four months post-randomization. Both types of cement are currently being used in the NHS. In light of this, we do not anticipate many unexpected serious adverse events (SAEs) associated with either treatments.

Foreseeable SAEs will be recorded in the "complication" section of the CRF and/or patient questionnaires. When the local research team becomes aware of an unexpected SAE in a trial participant, the principal investigator (PI) will review the SAE locally and make a decision about the relatedness of the event to the intervention. Any SAEs that are considered to be unexpected but potentially related to the intervention will be reported to the central trial team within 24 hours of the PI becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator or delegate (Nominated Person). SAEs that are deemed to be unexpected and related to the trial will be reported to the Research Ethics Committee within 15 days. All such events will also be reported to the Trial Steering Committee (TSC) and Data and Safety Monitoring Committee (DSMC) at their next meetings.

Outcome measures. Outcome measures will be collected in addition to the routine NHFD dataset which are collected at baseline and 120 days post-fracture. This timepoint will also be used to collect information regarding any infection which occurred in the 90 day post-surgery.

Primary outcome measure

The primary outcome measure for this study is deep SSI as defined by the Centers for Disease Control and Prevention definition of a "deep surgical site infection", that is a wound infection involving the tissues deep to the skin that occurs within 90 days of surgery.²⁴

Medical records for all patients will be reviewed by appropriately trained staff for indicators of infection at the time of the patient's discharge from the recruiting centre or at 90 days if the patient is still in the hospital. In addition, patients who have left hospital will self-report (via telephone interview, electronic media, or postal questionnaire at 120 days after surgery) any symptoms

or signs of infection. For those patients lacking capacity, an appropriate proxy will be asked to provide this information.

Upon indication of potential signs of infection at 120 days by the patient or proxy, the research team at the recruitment centre and/or GP will be asked to review the patient's medical records to confirm the signs of deep SSI in the period between discharge and 90 days post-surgery.

The recruitment centres will be asked to provide, if available, copies of any medical documentation, reoperation records, antibiotic details, microbiology reports, and imaging reports for any deep imaging that occurred in relation to suspected infection. These data will be collated by the central trial team in Oxford. The medical records of patients who died prior to 90 days post-surgery will be reviewed by the local research team to establish whether deep SSI have a contributory role to their death.

An independent outcome classification committee will convene to confirm the robustness of the above reporting system for identifying deep SSI. This committee will be given access to all the data collected by the research team as well as relevant, redacted sections of the patient's medical records as required. It will review all cases deemed to have a deep infection as well as a purposeful sample of 50 cases where no infection was reported. If the independent outcome classification committee finds any inconsistencies in the reporting of deep infection, this will be fed back to the recruitment centre with further training, as appropriate.

Secondary outcome measures

UK Core Outcomes Set for hip fractures. The EuroQol 5D-5L (EQ-5D-5L) is a measure of health-related quality of life, consisting of a five-dimension health status classification system and a separate visual analogue scale.²⁵ Responses to the health status classification system will be converted into multi-attribute utility scores, using the algorithm developed by van Hout et al²⁶ to generate supplementary utility values that are comparable with those derived from the EQ-5D-3L instrument, if the 5 L value sets that are recommended by NICE are not available at the time of the analysis. The EQ-5D-5L will be completed by a patient's proxy in the case of impaired capacity. This measurement will be taken at baseline and at 120 days post-surgery.

Mobility will be reported by participants or their proxy using an ordinal scale as per the NHFD: freely mobile without aids; mobile outdoors with one aid; mobile outdoors with two aids or a frame; some indoor mobility but never goes outside without help; and no functional mobility using the lower limbs. This will be captured on CRFs at baseline and 120 days postoperatively.

Residential status will be reported by participants or their proxy using an ordinal scale as per the NHFD: own

home/sheltered housing; residential care; nursing care; rehabilitation unit – hospital bed in the current trust; rehabilitation unit – hospital bed in another trust; rehabilitation unit – NHS funded care home bed; and acute hospital. This will be captured on CRFs at baseline and 120 days postoperatively.

Mortality will be recorded at discharge from the research site as well as in the 120 day follow-up. Sites or consultees may also report mortality at any point in the time between discharge and 120 days.

Antibiotic prescription rates. Antibiotic prescription information for wound healing complications other than deep SSI in the first 90 days will be obtained from the patient, consultee, or carer at the four-month (120-day) follow-up. The trial team may contact the patient's GP for information if the patient entered the trial under nominated consultee agreement and this information is not available from a carer.

Resistance patterns of infections. All wound infections will be assessed for antibiotic resistance profiles by the local microbiology team. Local reports of micro-organisms including sensitivities to antibiotics will be recorded on CRFs at discharge and/or 120 days post-surgery.

Complications. Complications other than surgical site infection will be recorded in the "complication" section of the CRF and/or patient questionnaires at discharge and 120 days.

Resource use. Resource use involving differences in surgical treatments between the two intervention groups will be obtained from CRFs that would be completed by the local research teams. Broader resource utilization will be captured through CRFs and patient questionnaires administered at baseline and four months post-randomization.

Power and sample size. Sample size was calculated on a superiority design. An absolute reduction in deep SSI of 1.5% in the intervention group is considered clinically important for the expected 3% deep SSI rate in the control group.¹⁵ This would result in 15 fewer deep infections per 1,000 hip fracture surgeries performed, which is a relative reduction in SSI of 50%. A total of 4,106 participants will be required to provide 90% power and 5% (2-sided) significance to detect a 50% relative reduction in deep SSI rate at 90 days.

As some participants will be entered into the trial under consultee agreement and may subsequently decline participation or die prior to providing baseline data we have inflated the sample size by 16.5% to compensate for this and other types of loss to follow-up. Allowing for 16.5% loss to follow-up at the 90 day primary endpoint leads to an overall target of 4,920 participants (2,460 per arm).

Recommendations for changes to the final sample size may be made to the independent DSMC and TSC if the overall loss to follow-up, or the infection rate is different to the rate anticipated.

Statistical analysis. A separate statistical analysis plan (SAP) with full details of all statistical analyses planned for the data of this study will be finalized prior to any primary outcome analysis. The SAP will be reviewed and will receive input from the TSC and DSMC. All statistical analyses will be reported following CONSORT guidelines for randomized controlled trials and the relevant extensions.²⁷ The primary analysis will be carried out on the intention-to-treat population, where all patients will be analyzed in the group they were randomized to.

The primary analysis will investigate differences in the primary outcome measure, the proportion of patients with deep infection, at 90 days post-surgery. Randomization stratified by centre should ensure balance between the treatment arms by centre. The primary analysis will be undertaken using a mixed effects logistic regression analysis adjusting for centre as a random effect to allow for any heterogeneity between centres. Supplementary analyses will also adjust for further important prognostic factors known to be related to outcomes. Proportions of deep SSI in each treatment arm will be reported with the difference between groups presented as an odds ratio, with 95% confidence intervals and p-values.

Secondary outcomes will be analyzed using analogous mixed effects linear (for continuous variables) or logistic (for binary variables) regression analysis, including a random effect for recruitment centre.

Missing data will be minimized by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis. The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate, multiple imputation will be used to avoid biases associated with complete case analyses. The analyses for the primary and key secondary outcomes will be repeated for the per protocol population (patients excluded from the per-protocol population will be pre-specified in the SAP as a sensitivity analysis to test the robustness of the results). Further sensitivity analyses will be undertaken assessing the underlying missing data assumptions and different definitions of deep infections.

Economic analysis. A within-trial economic evaluation will be conducted from a NHS and personal social services perspective in the first 120 days after randomization in the base case analysis as recommended by NICE.²⁸ Primary research methods will be adopted to estimate the costs of the surgical treatments, inpatient care (further treatment due to wound infection), outpatient

care (physiotherapy), community care (physiotherapy), home adaptations, and informal care. Unit costs for health and social care resources will largely be derived from local and national sources and estimated in line with best practice. Costs will be standardized to current prices where possible.

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, will be performed. Results will be presented using incremental cost-effectiveness ratios (ICERs), net monetary benefit, and cost effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping will be plotted.

Multiple imputation methods will be used to impute missing data and avoid biases associated with complete case analysis. Sensitivity analysis such as extending the study perspective (i.e. societal perspective which will incorporate informal care provided by participant's caregivers) and assessing the impact of missing data using complete case analysis will be conducted to explore its impact on the ICERs.

Data management. Personal data collected during the study will be handled and stored in accordance with the 1998 Data Protection Act, which requires data to be de-identified as soon as it is practical to do so.

The initial data collection and management tool used for these data was the OpenClinica open source software v. 3.14 (OpenClinica LLC and collaborators, Waltham, Massachusetts, USA). During the course of the study, all data were migrated to the REDCap electronic data capture tools hosted at The University of Oxford.²⁹

Trial organization and oversight. The day-to-day management of the trial will be the responsibility of the trial manager, based at Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and supported by the OCTRU staff. This will be overseen by the trial management group that will meet monthly to assess progress. It will be the responsibility of the trial manager to undertake training of the research associates at each of the study centres. The study statistician and health economist will be closely involved in setting up data capture systems, design of databases, and clinical reporting forms.

A TSC and a DSMC will be set up. The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required, critical endpoints of a clinical trial. The DSMC will advise the TSC and will adopt a DAMOCLES charter, which outlines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, review accruing data and summaries of the data presented by treatment group as well as consider emerging evidence from other related trials or research and review related SAEs that have been reported. DSMC

meetings will be held at least annually during the recruitment phase of the study.

Quality control. Quality control procedures will be undertaken to ensure integrity of consent, randomization, study entry procedures, and data collection. The clinical trials unit has a quality assurance manager who will monitor this trial by conducting regular inspections of the trial master file. The research will be conducted, generated, recorded, and reported in compliance with the protocol, GCP, and ethics committee.

Dissemination. The results of this trial will be disseminated to the hip fracture clinical community via presentations at national and international meetings. A manuscript for a peer-reviewed journal will be prepared and the results shared with patients via local mechanisms at participating centres.

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Author contributions:

- N. R. Agni: Developed the protocol, Managed the trial, Wrote the manuscript.
- M. L. Costa: Developed the protocol, Managed the trial, Wrote the manuscript.
- J. Achten: Developed the protocol, Managed the trial, Reviewed the manuscript.
- H. O'Connor: Developed the protocol, Reviewed the manuscript.
- M. E. Png: Developed the protocol, Wrote the manuscript.
- N. Peckham: Developed the protocol, Wrote the manuscript.
- S. Dutton: Developed the protocol, Reviewed the manuscript.
- S. Wallis: Developed the protocol, Managed the trial, Reviewed the manuscript.
- S. Milca: Developed the protocol, Managed the trial, Reviewed the manuscript.
- M. Reed: Developed the protocol, Managed the trial, Wrote the manuscript.

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Ethical review statement:

- Wales Research Ethics Committee 5 approved the trial on 3rd May 2018 (18/WA/0154).

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