Strategies to improve recruitment rate to the WHiTE 8 trial and investigating the effectiveness and safety of the use of antibiotic loaded bone cement in hip fractures.

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Abstract

Background

Hip hemiarthroplasty is commonly performed in hip fractures. Strategies to reduce surgical site infection (SSI) should be evaluated through randomised control trials (RCT). Additionally, strategies to improve recruitment rate to trials need to be investigated to improve efficiency and reduce research waste.

Aims

This thesis investigates the effectiveness of antibiotic loaded bone cement (ALBC) in hip fractures and safety on the risk of acute kidney injury (AKI). Additionally, it investigates two strategies to improve recruitment rate to the WHiTE 8 trial.

Methods

I conducted a cohort study on hip fracture receiving a cemented hemiarthroplasty and analysed the effect of different gentamicin containing systemic and ALBC regimens on AKI rate.

In my factorial RCT I evaluated two interventions; an enhanced trainee principal investigator (TPi) package and a digital nudge to determine the effect on recruitment rate to the WHiTE 8 trial.

Finally, I evaluated the use of ALBC in hip fractures through a systematic review.

Results

There were no differences in AKI rates between differing gentamicin systemic and ALBC regimens in hip fractures receiving a cemented hemiarthroplasty.

My factorial RCT showed benefit on recruitment (IRR 1.23 95% 1.09 to 1.40, p=0.001) from utilizing an enhanced TPi education intervention. The digital nudge intervention had no impact on recruitment (IRR 0.89 95% CI 0.79 to 1.01, p=0.07).

My systematic review showed that ALBC were shown to be favourable over plain bone cement for SSI prevention but there were mixed results when comparing different gentamicin concentrations in ALBC.

Conclusions

This thesis supports the use of low dose single ALBC, though, further RCTs are needed to determine if high dose dual ALBC confers any added benefit in SSI prevention.

Recruitment rate to RCTs can be improved with an enhanced TPi package. There are mixed results with a digital nudge intervention and should be used cautiously used in RCT trial design.

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Abbreviations

ADQI	Acute Dialysis Quality Initiative
AF	Atrial fibrillation
AIDS	Acquired immune deficiency syndrome
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALBC	Antibiotic loaded bone cement
ANOVA	Analysis of Variance
APi	Associate Principal investigator
ARCP	Annual review of competency progression
ARF	Acute renal failure
ASA	American Society of Anaesthesiologists
BOTA	British Orthopaedic Trainee Association
CCT	Certificate of Completion of Training
CDC	Centers for Disease Control and Prevention
CI	Chief Investigator
COPD	Chronic obstructive pulmonary disease
CORNET	Collaborative Orthopaedic Research Network
CTU	Clinical Trial Unit
ESKD	End stage kidney disease
GBD	Global Burden of Diseases
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HDDAC	High dose dual antibiotic cement
HES	Hospital Episode Statistics
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HSA	Health Security Agency
HTA	Health technology assessment
HTN	Hypertension
IDDM	Insulin dependent diabetes mellitus
IHD	Ischaemic heart disease
IQR	Interquartile range
IRR	Incidence rate ratio
ISRCTN	International Standard Randomised Controlled Trial Number
ITS	Interrupted time series
IV	Intravenous
JCST	Joint Committee on Surgical Training
KDIGO	Kidney Disease: Improving Global Outcomes
LDSAC	Low dose single antibiotic cement
MAR	Missing at random
MCAR	Missing completely at random

MMA	Methyl methacrylate
MNAR	Missing not at random
MRC	Medical Research Council
MSIS	Musculoskeletal Infection Society
NAR	Norwegian Arthroplasty Registry
NHCT	Northumbria Healthcare NHS Foundation Trust
NHS	National Health Service
NICE	National Institute for Health and care Excellence
NIDDM	Non-insulin dependent diabetes mellitus
NIH	National Institute of Health
NIHR	National Institute for Health and Care Research
NOS	Newcastle-Ottawa Scale
NUH	Nottingham University Hospitals NHS Trust
OCTRU	Oxford Clinical Trials Research Unit
OR	Odds ratio
PBC	Plain bone cement
PE	Pulmonary embolus
PHE	Public Health England
PI	Principal Investigator
PJI	Prosthetic joint infection
PMMA	Poly methyl methacrylate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	Peripheral vascular disease
RCT	Randomised control trial
REC	Research Ethics Committees
RRT	Renal replacement therapy
SMS	Short Message Service
SSI	Surgical site infection
SWAT	Study within a trial
THR	Total hip replacement
TKR	Total knee replacement
TPi	Trainee Principal investigator
WHiTE	World Hip Trauma Evaluation

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Author declaration

I declare that this thesis presents original work, and I am the sole author. Any collaborative work has been made explicit through this thesis. I can confirm that work from this thesis has not been previously submitted for any other degree or qualification at this University or any other educational institution.

Original work from this thesis has been disseminated in journals as below:

Agni N, Fairhurst C, McDaid C *et al.* Protocol for a factorial randomised controlled trial, embedded within WHiTE 8 COPAL, of an Enhanced Trainee Principal Investigator Package and Additional Digital Nudge to increase recruitment rates [version 1; peer review: 2 approved]. *F1000Research* 2019, **8**:1153 (https://doi.org/10.12688/f1000research.19743.1)

Agni N, Fairhurst C, McDaid C, Reed M, Torgerson D. EnTraP: A factorial randomised controlled trial embedded within world hip trauma evaluation eight COPAL investigating the effect of an enhanced trainee principal investigator package and digital nudge on recruitment rates. Research Methods in Medicine & Health Sciences. 2022;3(2):33-41. doi:10.1177/26320843211061297

The national multicentre study WHiTE 8 trial was only possible due to multi-disciplinary collaborative effort. This forms the host trial for my embedded studies in chapter 3. I have outlined my contribution to the trial and listed the resultant publications below.

Areas to the trial I led, developed, and delivered:

- Lead Trainee and proxy chief investigator to Professor Reed
- Funding agreement and contract development with industry funders
- Collaborative contract formation between sponsor and University of Oxford
- Responsibility with overall trial budget, allocation, and management
- Clinical liaison between recruitment centres and trials unit
- NHS REC submission process
- Northumbria hospital R&D liaison and site principal investigator
- Site initiation visits for site set up
- Independent outcome committee for primary outcome protocolisation, recruitment and management
- First draft and revisions of protocol publication

- Reporting the trial and writing the main results paper (co-first author with Professor Costa)
- Presentation of trial at BOA, AAOS and NIHR RCT trials meeting conferences.

Areas to the trial led by others but which I actively contributed

- WHiTE 8 ethics application
- Protocol editing, review and finalisation
- TMG attendance as representative and proxy to Chief investigator Mike Reed
- Day to day trial management
- Health economic publication for WHiTE 8 trial

Publications from the WHiTE 8 trial:

Agni NR, Costa ML, Achten J, et al. 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. Bone Jt Open. 2021;2(2):72-78. doi:10.1302/2633-1462.22.BJO-2020-0174

Agni, Nickil R et al. High-dose dual-antibiotic loaded cement for hip hemiarthroplasty in the UK (WHiTE 8): a randomised controlled trial. The Lancet, Volume 402, Issue 10397, 196 – 202

Png ME, Costa M, Nickil A, Achten J, Peckham N, Reed MR. Cost-utility analysis of dual-antibiotic cement versus single-antibiotic cement for the treatment of displaced intracapsular hip fractures in older adults. Bone Joint J. 2023;105-B(10):1070-1077. doi:10.1302/0301-620X.105B10.BJJ-2023-0633

1 Chapter 1: Introduction

Fragility hip fractures are a significant global burden with hip fractures accounting for 0.1% of worldwide disease (Johnell and Kanis 2004). The most up to date evidence using data from the Global Burden of Diseases (GBD) 2019 summarises the key burden of hip fractures worldwide (Feng et al. 2024). It is reported that the incidence of hip fractures in patients aged 55 and over in 2019 was 681.35 (95% CI 508.36 to 892.27) per 100,000 population. This represents a 24% increase since 1990 with the highest incidence being in three regions: Australia, Western Europe, and high-income North America. In terms of cause of fracture, the highest incidence rates were attributable to a fall (557.42 per 100,000 population, CI 397.88 to763.32) and contributed up to 85% of hip fracture numbers. The growing elderly population is projected to steadily increase demand for hip fracture treatment with estimations of around 100,000 patients annually by 2033 in England. (White and Griffiths 2011). The UK annual total hospital costs for fragility hip fractures have been estimated to be over £1.1billion thus placing a significant economic burden on society (Leal et al. 2016).

The standard of care for patients with hip fractures is usually surgical treatment unless the patient is not expected to survive a surgical procedure due frailty or co-existing medical problems. Surgery for hip fracture can result in complications, which can have unintended consequences of morbidity and mortality for patients. There are numerous strategies targeted at patients to minimise their risks of complication before, during and after surgery. One of the most significant complications is that of surgical site infection (SSI) and part of this thesis will be to focus on the prevention of SSI by using intraoperative antibiotic loaded bone cement (ALBC). As part of a research group from Oxford Clinical Trials Research Unit (OCTRU), I have collaboratively conducted a large-scale UK wide randomised clinical trial investigating the use of high dose dual ALBC for the prevention of surgical site infection in hip fractures; the WHiTE 8 trial. This thesis will focus on strategies to improve recruitment rate to this trial and provide supplementary safety evidence on patient kidney function when ALBC is utilised. I shall also evaluate by systematic review the current evidence, including the WHiTE 8 trial, on the use of ALBC in hip fractures for SSI prevention.

This chapter will introduce key orthopaedic concepts and terminologies regarding the surgical treatment of hip fracture. I will outline current UK standard practice in the treatment of hip fractures both in terms of surgery and antibiotic prophylaxis. I will then outline the WHiTE 8 trial as this is the host trial that underpins the rationale for this thesis and then discuss the structure and aims of this thesis. Further specific introductory detail is provided before individual chapters.

1.1 Key orthopaedic concepts

1.1.1. Hip arthroplasty

Arthroplasty is the surgical replacement of a joint surface which achieves pain relief and functional restoration. There are two populations who present to the hospital who receive hip arthroplasty: elective and trauma populations. Whilst the differences are outlined below, it is important to note that in this thesis, the trauma population of interest are those receiving a partial hip replacement (hemiarthroplasty) after a type of fragility hip fracture called a neck of femur fracture.

Elective patients attend with chronic pain and functional loss in one or more joints due to a multitude of reasons which may include congenital conditions, infection, chronic trauma, inflammatory arthropathy with the most prevalent reason being osteoarthritis. In this population, the most common procedure that is undertaken is a total hip replacement (THR). The procedure replaces both sides of the hip joint: the femoral head and the acetabulum i.e., ball and cup.

Trauma patients undergoing arthroplasty present via an emergency admission with the most common cause being a fall resulting in a neck of femur fracture. When a hip fracture occurs within the region that carries the blood supply to the femoral head (intracapsular fractures), fixation of the hip is often not a recommended treatment modality due to the loss of blood circulation to the head of the femur resulting in necrosis of the head. At this point, the treating surgeon will decide between a total or partial hip replacement. A hemiarthroplasty replaces only the femoral head and leaves the acetabulum intact. The decision between a THR and hemiarthroplasty is based on National Institute for Health and Care Excellence (NICE) recommendations that take into account mobility status, cognitive impairment and medical comorbidities (NICE 2023). The 2016 National Hip Fracture Database (NHFD) annual report stated that 31.4% of patients who had displaced intracapsular fractures received a THR (Boulton, Johansen, and Wakeman 2016).

During a THR or hemiarthroplasty procedure the femoral stem (and acetabular cup for THR) are either fixed into place by uncemented or cemented techniques. Current NICE recommendations are that patients with a hip fracture requiring arthroplasty receive a cemented prosthesis (NICE 2023). These guidelines are followed relatively compliantly as the 2016 NHFD reported a cemented arthroplasty rate of 88.9% (Boulton, Johansen, and Wakeman 2016). During a cemented hemiarthroplasty procedure, patients receive antibiotics via two routes for prophylaxis against surgical site infection (SSI). The first will be intravenously immediately prior to surgical incision. The second dose will be delivered locally over a prolonged time-period through the bone cement (used to fix the prosthesis) which is impregnated with antibiotics.

1.2 Antibiotic loaded bone cement

Polymethylmethacrylate (PMMA) bone cement was first used in 1943 after a patent by Degussa and Kulzer, who discovered that the dough formed from a PMMA powder and liquid monomer methyl methacrylate (MMA) hardens with the addition of benzoyl peroxide (Bistolfi et al. 2019). Whilst initially used in dental fixations, bone cement has been used for fixation of artificial joint prosthesis for over 65 years with English surgeon Dr. John Charnley being credited for the first use in orthopaedics (CHARNLEY 1964). The first commercial cements were released in the 1970s with those available included Palacos, CMW, Surgical simplex and Zimmer bone cements. These are still in use today with unchanged chemical compositions (Walenkamp and Argenson 2007).

A surgical site infection (SSI) is a significant morbidity of joint arthroplasty with reported rates in hip hemiarthroplasty of up to 7.3% and 1-year mortality attributed to infection being up to 50% (Dale et al. 2011; Guren et al. 2017; Edwards et al. 2008; Noailles et al. 2016). Systemic antibiotics have been shown to be effective in decreasing infection rate in total hip replacements (Hill et al. 1981) but despite this technique SSI rates remain a concern. The majority of SSI organisms seed at the time of surgery through airborne contamination (Brown, Taylor, and Gregg 1996; Lidwell et al. 1983), with bacterial adhesion to the implant occurring in the form of a biofilm. This biofilm proves difficult to eradicate due to poor penetration of systemic antibiotics and often requiring removal of implant as it shows resistance to humoral, and cell mediated activity (Zoubos, Galanakos, and Soucacos 2012; McConoughey et al. 2014).

An approach to SSI prevention is a system of local antibiotic delivery around implanted prosthesis, using ALBC to prevent bacterial adhesion and thus biofilm formation. This mode of delivery allows for higher local concentrations of the antibiotic without causing systemic upset (Passuti and Gouin 2003). Heraeus Kulzer GmbH have developed numerous types of commercial ALBCs including Palacos R+G and Copal G+C; both used in the WHiTE 8 trial outlined further in this thesis.

From a Medline index literature search undertaken in November 2017 there were no randomised control trials (RCT) or observational database analyses that could be found looking specifically at differences in SSI by route of antibiotic prophylaxis in hip hemiarthroplasties. Therefore, I used the closest population (THRs) and looked at the evidence basis to draw inferences.

There is mixed evidence on the effect of ALBC in reducing SSI in primary hip arthroplasty. Registry studies from both Norway and Sweden have shown that the use of ALBC is effective in reducing SSI. In a review of 22,170 primary total hip replacements between 1981-2001 from the Norwegian Arthroplasty Register (NAR) the lowest risk of revision was found in patients who received both

parenteral and local antibiotics. Those who received antibiotics systemically in isolation had a 1.4 times higher revision rate (95% CI 1.1 to 1.7, P<0.001) (Engesæter et al. 2003). Similar results were found in a Swedish prospective multicentre study involving 92,675 THRs between 1978 to 1990. The Poisson models of influences on risk of revision was significantly lower with the use of Gentamicin containing bone cement (p<0.001) (Ahnfelt et al. 1990). A meta-analysis of 24,661 THRs of 6 comparative studies showed that the use of ALBC reduced deep infection rates from 2.3% to 1.2% (Parvizi et al. 2008). However another systematic review of 30 RCTs (primary hips and knees), of which 10 were included in the meta-analysis, found that preoperative intravenous antibiotics significantly reduced infection rates but showed no statistically significant difference when compared to the use of ALBC (Voigt, Mosier, and Darouiche 2015). There were only two studies included in this subgroup analysis in THR with a risk ratio of 0.8 (95%CI 0.6 to 1.08, p=0.15). They suggested that the use of antibiotics is the most important factor in reducing SSI risk and that route of administration may not have an impact.

Antibiotic loaded bone cement is used both as surgical prophylaxis for SSI but also in the treatment of patients with confirmed prosthetic joint infections (PJIs). When used therapeutically, the bone cement is used in one of two ways: an industrially manufactured bone cement pre-loaded with high dose antibiotics, or a customised addition of antibiotics to a bone cement by the surgeon. Surgeons often use the latter option due to the ability to individualise the treatment protocol for patients who may demonstrate a microorganism profile where industry manufactured options may be sub optimal due to resistance (Frew et al. 2017). The disadvantages of customised addition of antibiotics by the surgeon are that there are no guarantees for uniform distribution of antibiotics across the cement and the elution characteristics become unpredictable and nonreproducible. In vitro trials have shown significantly greater post-operative elution rates compared to commercial cements and numerous reports have shown that “home-made” cements have led to increased risk of acute kidney injury (AKI) as a result in the septic revision population (Frew et al. 2017; Edelstein et al. 2018; James and Larson 2015).

Since ALBC and systemic antibiotics have the potential benefit of reducing SSI rates in THR, inferences can be made that the same holds true in the neck of femur population receiving a hemiarthroplasty. This is also shown by current standard UK practice in this cohort of patients receiving antibiotics via bone cement (when used) and parenteral administration. There are however no guidelines or recommendations to justify this practice. There is therefore a need for a systematic review in the hemiarthroplasty population to determine the effect of ALBC on SSI rates.

1.2.1 Aminoglycoside antibiotics

Aminoglycosides are a class of bactericidal drugs used commonly in orthopaedic surgery. They include drugs such as gentamicin and tobramycin and target protein synthesis in susceptible organisms. They are a highly effective group of antibiotics which have the advantage of being cost effective and exhibit

both wide antimicrobial spectrum and stability when used in bone cement (Anagnostakos and Kelm 2009; Anagnostakos 2017). The disadvantages of multiple doses have been well documented in the literature and include the potential for hearing loss (ototoxicity) and acute kidney injury (AKI) (Meyer 1986; Buring et al. 1988; Ariano, Zelenitsky, and Kassum 2008; Black, Pesznecker, and Stallings 2004).

There is mixed evidence for AKI and the use of gentamicin when used for elective hip and knee surgery (total hip and total knee replacement). When considering how gentamicin prophylaxis either systemically or via ALBC effects the AKI rate in the trauma hip hemiarthroplasty population a PubMed search in August 2018 ("Gentamicin" and "hemiarthroplasty") reveals no relevant studies. There is therefore a potential gap in the evidence that needs to be addressed. The studies outlined below were identified from a literature search on the use of gentamicin in arthroplasty patients.

A systematic review and meta-analysis of surgical prophylaxis with intravenous gentamicin and its effect on AKI was conducted by a team in New York (Srisung et al. 2017). There were no RCTs found in the electronic searches. Eleven prospective and retrospective studies with fifteen cohorts including 18,354 patients were included in the analysis. The gentamicin doses ranged from fixed single doses of 120 to 240mg or doses based on body weight ranging from 1.5mg/kg to 4mg/kg. The findings were that a gentamicin containing regimen carried significant risk of patients developing post-operative AKI in orthopaedic surgery (fracture neck of femur, THR and TKR) with a risk ratio of 2.9 (95% CI 1.84 to 4.88), however, the degree and severity of the AKI was reported as mild and transient. Another systematic review of thirty six studies looking at adverse effects of single dose intravenous gentamicin ranging from 1mg/kg to 480mg showed mild and/or transient effects on renal function and also reported no cases of ototoxicity (Hayward et al. 2018). This study included 11 RCTs, 18 cohort studies, one retrospective survey, three pharmacokinetic studies and three quasi-experimental studies and there were 20 studies where surgical prophylaxis was the indication for gentamicin.

A prospective cohort study published after the above reviews included patients undergoing elective knee and hip arthroplasty. They divided their participants into two antibiotic regimen groups: cementless hips and knee arthroplasties received both intravenous cefuroxime with 1.5mg/kg gentamicin, and cemented hips received intravenous cefuroxime with gentamicin containing bone cement (Palacos R+G). In this study of 2755 patients there were no differences in AKI rates between antibiotic regimens but a multivariate analysis model showed a two-fold increase in AKI for those patients undergoing lower limb arthroplasty regardless of the method of gentamicin administration; intravenously or via ALBC (odds ratio [OR] 2.12 [95% CI 1.979 to 34.968]; P = 0.004 and OR 1.82 [95% CI 1.430 to 26.991]; P = .015, respectively) (Tucker et al. 2018). The study reported that 31 of the 32 patients experiencing AKI had stage one dysfunction which resolved rapidly and did not effect length of stay.

Another study published after the above reviews was a small pharmacokinetic randomised controlled trial of 15 patients undergoing a total hip replacement (THR) compared ALBC containing 0.5g to 1g of gentamicin. Systemic antibiotics were not used peri-operatively in any of these patients. The maximum serum concentrations of gentamicin in the higher dose group (0.96-2.90µg/ml) were found to be two to three times the concentrations of the low dose ALBC group (0.34-1.45µg/ml) at 30 min post cement implantation although, never reaching a serum concentration associated with renal toxicity (Wahlig et al. 1984).

Two further studies reported increased AKI rates when intravenous flucloxacillin has been administered in conjunction with gentamicin. There is thought to be a synergistic nephrotoxic environment created form dual administration. The first, an observational study of 1588 patients comparing different regimens of antibiotic administration and showed the highest incidence of AKI at 13% when both antibiotics were given intravenously. The incidence was 8.5% when the gentamicin was used in the form of Palacos bone cement (Graham et al. 2021). The second, a cohort study of 238 patients reported an AKI incidence of 9.45% when flucloxacillin and gentamicin were administered intravenously together (Bailey et al. 2014).

Although the systematic reviews identified have not been recently updated, the existing evidence on the use of aminoglycosides in the elective population results in transient or minimal clinical impact on risk of AKI unless used in a regimen with flucloxacillin. It is unknown whether these findings can be extended to patients who have a hemiarthroplasty for a neck of femur fracture. This population tend to be frailer with numerous comorbidities and thus research is needed to determine whether the use of gentamicin when used systemically +/- in ALBC has an impact on rates of AKI.

1.3 WHiTE 8 trial

The WHiTE 8 trial formed the host trial for this thesis and is summarised here. The investigator led RCT was sponsored by Northumbria Healthcare NHS foundation trust (NHCT) and run out of the Oxford Clinical Trials Unit (OCTRU) with industry funding by Heraeus Medical GmbH. As part of the core management team, I was the clinical lead trainee working with and in proxy to the chief investigators during the timeline of the trial (2018-2023) and this has been summarised in the authors declarations preceding this chapter.

This pragmatic multicentre trial was designed to be embedded in the WHiTE cohort using a network of established centres to recruit patients. The full protocol and results have been published (N. R. Agni et

al. 2021; Nickil R. Agni et al. 2023) and are provided in the appendix for reference (Appendix 7.1.1 and 7.1.2). A protracted summary of the trial is outlined below.

The WHiTE 8 trial involved 26 UK centres between August 2018 and August 2021. This pragmatic superiority trial included people of 60 years and older with a hip fracture undergoing a cemented hemiarthroplasty. Participants were randomised to either low dose single ALBC or high dose dual ALBC in a 1:1 ratio stratified by centre. Th low dose single ALBC contained 0.5g of gentamicin and the high dose dual ALBC contained 1g of gentamicin and 1 g of clindamycin. The primary outcome was deep SSI at 90 days post randomisation as defined by the US Centers for Disease Control and Prevention (CDC). Secondary outcomes included quality of life, mortality, antibiotic use and resistance patterns, mobility and residential status and cost effectiveness all assessed at 120 days.

The target sample size calculated to detect an absolute reduction in deep SSI at 90 days of 1.5% (from 3% to 1.5%). From the previous experience of trials involving this population, OCTRU recommended the inflation of 16.5% to the sample size to account for loss to follow up. Hence, achieving 90% power with 5% two-sided significance required a sample size of 4920 participants. Whilst originally planned to complete recruitment by February 2020 the resultant effect of covid on halting research teams at multiple sites meant that there was almost 6-month delay for completion of recruitment and final follow up being in January 2022.

Further consideration with regards to the results and how it sits within the body of current evidence is discussed in the systematic review I carried out (Chapter 4).

1.3.1 Supplementary safety evidence for WHiTE 8 trial

The quasi-randomised study that preceded the WHiTE 8 trial was a single organisation study (two hospitals) that showed a significant reduction in SSI between low dose single ALBC and high dose dual ALBC (Sprowson et al. 2016). However, there was an interesting potential confounder which was highlighted in the study, which was the reduced dose of prophylactic gentamicin that was given intravenously due to higher gentamicin dose that patients were receiving in the high dose dual ALBC.

As described in section 1.2.1., gentamicin is an aminoglycoside that can potentially be nephrotoxic in higher doses. At the time of inception of this PhD (Jan 2018), I searched PubMed for literature evaluating the nephrotoxicity from combined use of gentamicin intravenously and in ALBC in patients receiving a hemiarthroplasty for intracapsular fracture. There were no studies that could be found to answer this question. Numerous hospitals use gentamicin as part of their intravenous surgical prophylaxis for SSI and therefore it was an important question that needed to be considered with the

WHiTE 8 trial embarking in several centres in the UK, ultimately with potentially practice changing result of the trial in the treatment of hip fractures.

The research reported in chapter 2 provides additional safety evidence to supplement the WHiTE 8 trial. The NHCT had records of all hemiarthroplasties done over a 10-year period with changes in antibiotic prophylaxis protocols at different times in response to changing ALBC gentamicin content. This provided the best available readily accessible database to analyse to determine if there was any relationship between surgical antibiotic prophylaxis and rates of acute kidney injury.

1.4 Orthopaedic research

Trauma and Orthopaedics is the largest surgical speciality in the UK but has generally attracted a small proportion of available national and international funding for health research.(Rankin et al. 2014) Orthopaedic research output has also been limited by a lack of structured academic training within the speciality and research traditionally deemed as lower priority by specialist registrars in contrast to clinical commitments (Rankin et al. 2014). The landscape is however changing, with more priority being placed on the formation of high-quality research. One successful example of delivering orthopaedic research has been through longitudinal cohort studies with multicentre orthopaedic collaborators to provide a framework for embedding randomised clinical trials (RCTs) for recruitment (Matthew L. Costa et al. 2016).

The modification of Certification of Completion of Training (CCT) criteria for surgical trainees to include research targets has led to a significant change and step in the right direction (JCST 2016). The UK Joint Committee on Surgical Training (JCST) guideline for CCT in orthopaedics now includes research as a core objective. All trainees must complete a Good Clinical Practice course in research governance along with evidence of research methods training or completion of a research methodologies course. Trainees must also evidence journal club activity through assessment, or a portfolio published reflection. In addition to these basic requirements a minimum of two further research requirements are necessary which includes a higher research degree (MSc, MPhil, MD, PhD), PubMed cited authorship, two national or international meeting presentations or recruitment to research ethics committee approved or multi centre observational studies. Advanced research evidence could be used as alternatives to the above through involvement with trainee research collaborative committee roles/projects, co-application for a clinical trial grant application or membership of a National Institute for Health and Care Research (NIHR) portfolio study management group.

Surgical Trainee collaboratives are run by trainees in a committee structure with the aim of completing regional and national multi-centre observational and randomised clinical studies. Numerous high-

quality projects have been published thus showing the power and success of a trainee led initiatives (Khaleeq, Kabariti, and Ahmed 2023; Jamjoom et al. 2016). Considering the extensive network of trainees in orthopaedic units nationally, interventions directed at supporting trainee-led trial recruitment has the potential to improve the performance of national clinical trials. Therefore, this has formed an area of focus in this thesis to embed an intervention directed towards trainees to improve recruitment rate in the WHiTE 8 trial (chapter 3).

1.4.1 Randomised clinical trials

Randomised controlled trials (RCTs) are considered the gold standard when evaluating the efficacy and effectiveness of health care interventions. The NIHR awarded £227 million of funding to 302 research projects in 2017-18 with a significant portion of this being awarded for RCTs (NIHR 2018). The results of these studies can be used by healthcare decision makers such as the UK's National Institute for Health and care Excellence (NICE) to guide policy and practice nationally.

There are an increasing number of pragmatic orthopaedic RCTs being conducted with regards to most clinical and cost effective treatment option for patients and NHS respectively (Matthew L. Costa et al. 2014; Sims et al. 2018; Handoll et al. 2015). The results of RCTs that test effectiveness (pragmatic trials) tend to be widely applicable with greater external validity as shown from the results of trials such as the UK DRAFFT trial (Matthew L. Costa et al. 2014, 2016). This is from the pragmatic approach taken in the trial design versus a highly controlled design which is more used in trials of efficacy (exploratory trials). Pragmatic trials tend to be multicentred, involve larger sample sizes and have less stringent inclusion criteria. The intervention is also often carried out in a less controlled environment and thus any intervention related outcome occurs in the context of "real world" practices; hence the generalisability (M. L. Costa et al. 2017; Porzsolt Franz et al. 2016). Recruitment is a challenge in these larger pragmatic trials and so strategies to improve recruitment to large RCTs forms one area of focus in this thesis.

The World Hip Trauma Evaluation (WHiTE) comprehensive cohort is an observational study collecting data on fractured neck of femurs (Matthew L. Costa et al. 2016). Within this cohort there have been many pragmatic RCTs embedded with numerous high impact publications; the WHiTE 3 Hemi trial, WHiTE 5 and WHiTE 8 trials (Sims et al. 2018; Fernandez et al. 2022; Nickil R. Agni et al. 2023). The WHiTE 8 trial (chapter 1.3) forms the host pragmatic RCT for the research questions that are posed in this thesis.

1.4.2 Studies within a trial

There is a limited evidence base regarding optimal trial design and trial processes (Treweek et al. 2018; Gillies et al. 2021). The Trial Forge initiative was created to increase the evidence base for trial deign and thus lead to more efficient methodologies to be applied in RCT design (Treweek et al. 2015). This one-day workshop starting in 2014 brought together 38 participants experienced in different aspects of trial processes to share knowledge and current evidence on key trial processes to create a methodology research agenda for researchers to collaborate and improve the evidence body.

One method of increasing the evidence base is by embedding a self-contained study in a host trial for the purpose of evaluating or creating new methods of conducting trial processes. This embedded methodology is known as a 'study within a trial' (SWAT). The SWAT Repository Store was created by a collaborative group including the Northern Ireland Network for Trials Methodology Research and Medical Research Council's Network of Hubs for Trial Methodology Research in the UK (Clarke et al. 2015). This resource can be used by researchers to identify and review existing SWAT protocols and furthermore to propose new SWAT protocols to contribute to the body of evidence to make informed decisions regarding research methodologies. Current registered SWATS cover a wide array of trial processes including site set up, recruitment, retention, data collection and data management. I utilised the SWAT repository to make sure that the interventions I was considering embedding into WHiTE 8 had not already been investigated to prevent duplication of research.

1.4.3 Recruitment to trials

About half RCTs struggle with the recruitment of clinicians and patients and subsequently fail to reach their target sample size. This has the potential to lead to under powering of the trial and consequently jeopardises the validity of the reported results. Many trials are forced to extend trial timelines for recruitment; however, this leads to increased trial management costs and is therefore not always feasible. Several trials alternatively have revised their sample size downwards or had no option but to close prematurely due to poor recruitment. (McDonald et al. 2006; Bower, Wilson, and Mathers 2007). A 2022 review of 388 NIHR randomised control trials from 1997 – 2020 showed that 30% of trials modified target recruitment with 67% of them being downward (Jacques et al. 2022).

The challenge of recruitment to RCTs have been well documented in the literature. In the UK, only 55% of NIHR-funded trials run between 2002 and 2008 met their recruitment target, with 45% needing funding extensions (Sully, Julious, and Nicholl 2013). A cohort study of 114 trials (MRC and HTA-funded) found that only 31% achieved the original recruitment target, and 53% had to be extended (McDonald et al. 2006). Another review of 151 HTA funded trials between 2004 and 2016 also found a target sample size achieved in only 56% of studies (Walters et al. 2017). The problem is not only

limited to the United Kingdom as studies conducted in the United States also experiencing similar recruitment challenges. The US National Institute of Health (NIH) inventory surveyed 41 trials and found that 34% met their recruitment target while 24% failed to recruit more than half their planned target (Charlson and Horwitz 1984).

Strategies to improving recruitment to randomised control trials is therefore a significant target for further research. There have been randomised and quasi-randomised trials that have targeted methods of improving recruitment to RCT's and these form the basis of a 2018 Cochrane systematic review (Treweek et al. 2018). This review included healthcare, non-healthcare, hypothetical trials and excluded studies related to retention and evaluations of incentives and disincentives for clinicians to recruit participants.

Positive recruitment strategies that had a GRADE high level of certainty included open trial design (RD 10%, 95% CI 7% to 13%) and telephone reminders (RD 6%, 95% CI 3% to 9%). Bespoke participant information leaflets made little or no difference to recruitment (RD 1%, 95% CI -1% to 3%). Despite the 72 comparisons made in the systematic review, many were single studies with only seven meta-analysed in the systematic review. The authors suggested more replication for the purposes of meta-analysis rather than innovation and that the research community should prioritise recruitment interventions in most need of evaluation.

Amongst the 68 trials reviewed, 26 of these were hypothetical trials with 24 judged to have a high risk of bias as the decision to participate was not real. The results of hypothetical trials have a degree of uncertainty as participants may have made different decision when faced with a real choice. Considering the numerous examples of successful SWATs embedded in real trials the group had decided to exclude hypothetical trials from the next update of the review.

In addition, the intervention was targeted at recruiters to the trials in only five out of 68 studies with two studies having a high risk of bias and were not presented in the analysis. The interventions assessed were using a post card teaser campaign, trial centre coordination through on-site visits and an additional communication; none of which had an impact on recruitment rates (Lee et al. 2017; Monaghan et al. 2007; Liénard et al. 2006). The paucity of interventions targeted at recruiters highlights the need for further evaluation amongst this population and there is consensus regarding this. The PRioRiTy project, which ran a James Lind Alliance prioritisation process for recruitment methods research has published their prioritisation of important unanswered trial recruitment questions for research. 790 survey respondents identified 496 questions which were reduced to a list of top 20 questions which were then ranked in a face-to-face workshop. Four out of the top twenty questions were directed towards recruiters to trials (Healy *et al.*, 2018)

An earlier systematic review, focused on evaluating strategies aimed at increasing the recruitment activity of clinicians and found eight quantitative studies describing four interventions with three being trials (Fletcher et al. 2012). There were no improvements in recruitment by utilisation of nurses over surgeons or through greater communication from central trial coordinators with on-site monitoring. An interesting before and after study included in the review showed that a complex intervention directed towards nurses involving training, advice and personal feedback resulted in over 65% of eligible participants consenting to randomisation with increasing rates to 81% over the observational period (Donovan et al. 2009). The weakness identified by the authors of this study was that evaluation was only able to be done with observational techniques and further studies using randomisation would be needed to evaluate further.

A survey of 48 UK clinical trial unit (CTU) directors was carried out to investigate the range of interventions used to improve recruitment and retention (Bower et al. 2014). There were 23 individual responses from 18 CTUs (38%) from a range of staff including statisticians, trial managers, health researchers and research nurses. Table 1 highlights interventions used by CTUs to improve recruitment.

Table 1: Routinely used recruitment and retention methods at UK CTUs (modified from Bower et al 2014 (Bower et al. 2014))

PATIENTS	Formal patient information documentation e.g., design and translation Promotion e.g., media, advertising, and community sessions
RECRUITERS	Presentations and training about recruitment challenges
MONITORING	Recruitment staff reminders Reducing burden (randomising online in real time, contact numbers for queries, and simple case report forms)
INCENTIVES	Targets (site recruitment targets, competition, and feedback) Incentives (gifts for sites, co-authorship, monetary incentives)
HUMAN FACTORS	Relationships (face to face initiation, regular contact with recruitment staff and site champions)

Many of these interventions such as site champions and incentivising clinicians with non-financial benefits are routinely being used without formal testing thus creating opportunities to trial these hypotheses by nesting them in large RCTs (Treweek et al. 2018).

The results from the survey of CTUs were used to inform a workshop on interventions to improve recruitment and retention. Priorities for evaluation included training site staff, methods of communication with patients and incentivising site staff (Bower et al. 2014). It is also interesting to note that a systematic review of incentives and disincentives for clinicians to recruit to RCTs identified no RCTs of interventions hence highlighting the need for further work in this area.(Rendell, Merritt, and Geddes 2007)

1.4.4 Trainee principal investigators

Trainee Principal Investigators (TPis) also now known as associate principal investigators (APi) are often surgical trainees whose role it is to work alongside local site consultant principal investigators (PIs) in a research study. The principal aim of the role is to co-ordinate and engage local trainees in recruiting patients to the trial especially out of normal working hours. Several multicentre orthopaedic trials including DRAFFT2, WHiTE7 and KReBS (Matthew L. Costa et al. 2022; ISRCTN55305726 2017; Cook et al. 2019) have utilised surgical TPis at recruitment centres with anecdotal patient recruitment success, whilst TPis in the TrAFFix study (Griffin et al. 2017) seemed to make little anecdotal difference. There are possible detrimental effects on recruitment from TPis being utilised e.g., replacement or dilution of trained research nurses, increased protocol deviations and slower recruitment. A PubMed literature search I did in 2018 at the start of this PhD highlighted no RCTs looking at either a local site champion or TPi on recruitment rate to a trial. There were no registered protocols for SWATs in progress either in the SWAT repository. In addition, the evaluation of this TPi role from a trainee perspective had not been undertaken.

An increasing number of recruitment centres to orthopaedic trials (including WHiTE affiliated centres) are utilising some form of the TPi role thus providing challenges regarding evaluating the impact of the role itself. This may be through a role as described above or through regional trainee collaborative networks e.g., CORNET in the Northern Deanery aiming to increase trainee participation in research. Therefore, undertaking an embedded RCT with centres being randomised to receive or not the TPi intervention would not be possible due to these confounding issues causing contamination at the recruitment sites.

Within the WHiTE framework the TPi is recruited and managed locally and by the consultant PI. There was a TPi manual provided by the Oxford CTU with no further education or involvement centrally from the CTU. There was therefore potential to create an enhanced TPi role where formal initial education and ongoing support can be used to evaluate the impact on local recruitment rates. A systematic review of training programmes for recruiters to RCTs found that these programmes were well received and increased recruiters' self-confidence. There was no definitive conclusion on the impact on recruitment

rate and highlighted the need for further research in the area.(Townsend et al. 2015)

1.4.5 Nudging

Choice architecture interventions or otherwise known as nudges are being used increasingly to influence behaviour by public health policymakers and researchers. The behavioural concept of nudge theory is defined as follows:

"A nudge, as we will use the term, is any aspect of the choice architecture that alters people's behavior in a predictable way without forbidding any options or significantly changing their economic incentives. To count as a mere nudge, the intervention must be easy and cheap to avoid." (Thaler & Sunstein 2008, p. 6) (Thaler and Sunstein 2008)

Fundamentally, this is a way of influencing an individual's behaviour through an intervention without limiting their choice. This concept is used extensively in marketing, economics, and healthcare promotion. Successful examples of nudging include the traffic light system labelling on food items to promote healthy eating and text messaging to increase organ donation registry.(Thorndike et al. 2014; Cabinet Office Behavioural Insights Team 2013)

Digital nudging is used regularly in RCTs e.g., emails, recruitment league tables highlighting performance relative to other centres and certificates; however, at the time of inception of this thesis (2018) there were no PubMed publications regarding nudging's effect on recruitment. This therefore provided another focus of this thesis later described in chapter three.

1.5 Thesis aims and structure

In this thesis I aim to address these following four questions outlined here.

1. **Does the use of gentamicin in systemic prophylactic antibiotics +/- in antibiotic loaded bone cement lead to increased risk of acute kidney injury post operatively in patients with hip fracture receiving a cemented hemiarthroplasty?**

This question has been addressed in chapter two using a large observational dataset from a single NHS foundation trust. As identified in this chapter there is no evidence to answer this question in the trauma population with inferences drawn from a different population group (elective total hip replacements). Considering the planned recruitment population of nearly 5000 patients of the WHiTE 8 trial I felt this would be an important safety question to ask as it may have informed prophylactic antibiotic choice for those involved in recruiting to the trial. The observational study would fill a gap in the knowledge for this cohort of patients and inform antimicrobial prophylaxis practice at hospital site that use ALBC containing gentamicin along with systemic prophylactic doses.

2.

   a. **Can the recruitment rate of patients to the WHiTE 8 trial be improved by delivering a complex education intervention to trainee principal investigators?**

   b. **Can the recruitment rate of patients to the WHiTE 8 trial be improved by positively reinforcing recruiter behaviour after randomisation through an additional personalised email?**

There is existing evidence and a systematic review on studies within a trial that aim to make a difference to recruitment to a randomised control trial. There is however a gap in the evidence for interventions directed to trainee principal investigators who form an important part of modern orthopaedic RCTs. There are also no studies evaluating the effectiveness of a behavioural modification intervention with the aim of improving recruitment rates. Chapter three addresses this with a factorial trial embedded in to the WHiTE 8 trial and evaluates the questions asked above.

3. **What is current evidence for the use of antibiotic loaded bone cement in patients with hip fracture receiving a cemented hemiarthroplasty?**

At the time of starting this PhD it was identified that there was a need for systematic review available to address this question. The timing of the review was considered in terms of the availability of results from ongoing trials and ensuring the review summarised the complete evidence basis for the use of ALBC in patients who had intracapsular hip fractures. The only registered trial addressing this topic in August 2018 was the WHiTE 8 trial. I therefore decided that the best option would be to conduct a systematic review to address this question after completion of the WHiTE 8 trial in 2022. This is presented in chapter four of this thesis.

Finally, chapter five and six summarises, discusses, and concludes the findings of this thesis with recommendations for the direction of future research.

2 Chapter 2: The effect of antibiotic loaded bone cement with or without intravenous gentamicin on the rate of acute kidney Injury in patients with intracapsular hip fractures receiving a cemented hemiarthroplasty.

2.1 Summary

Background

Gentamicin has the potential to cause an acute kidney injury (AKI) in patients receiving a hemiarthroplasty after hip fracture when used either systemically or in conjunction with gentamicin containing antibiotic loaded bone cement (ALBC). Published evidence for this in the trauma population is limited and therefore further work is needed to evaluate the risk of AKI in hip fracture patients to guide surgical antimicrobial prophylaxis.

Aims

The primary aims of this study were to determine the rate of AKI as classified by the RIFLE criteria within five days post-surgery from differing doses of gentamicin in ALBC and intravenous gentamicin regimens. The secondary aims were to determine if there was a difference in 30-day admission rates to critical care unit for AKI and 30-day mortality rates.

Methods

This was an observational retrospective cohort study of hip fractures receiving a hemiarthroplasty between January 2008 and August 2018 using non-experimental analysis (before and after comparisons) as well as a quasi-experimental (interrupted time series) analysis methodology. The data used for this study is part of a prospectively collected dataset on all hip fractures that have been treated at Northumbria Healthcare NHS Foundation Trust. All hip fractures receiving a cemented hemiarthroplasty were included with exclusion of those with end stage renal dysfunction.

Results

A total of 3178 patients were identified with a complete renal dataset on 3129 patients that fit the inclusion criteria. Overall, both non-experimental and quasi-experimental showed no difference in rates of AKI between low dose and high dose gentamicin ALBC or in differing systemic doses of gentamicin. There was no difference in 30-day admission to critical care unit (P=0.307) but mortality at 30-days showed a statistical difference between low dose and high dose gentamicin containing ALBC (p=0.044) and was 8.6% and 6.5% respectively.

Conclusion

Higher doses of gentamicin administered to patients prophylactically via ALBC or systemically do not result in an AKI. Additionally, there are no adverse effect on mortality or admission to critical care and so can be used with reassurance in the treatment of patients with hip fractures receiving a cemented hemiarthroplasty.

2.2 Introduction

The purpose of this chapter is to explore the potential renal function complication theoretically possible from the use of higher doses of gentamicin in the treatment of patients with hip fractures who receive cemented hemiarthroplasties. This is a very relevant concern considering the increasing practice of using high dose antibiotic loaded bone cement (ALBC) in people undergoing cemented hemiarthroplasties. The conclusions of this chapter will provide additional safety advice to supplement the WHiTE 8 trial and inform the future update of the NICE guidelines (NICE 2023) on the treatment of hip fractures requiring a cemented hemiarthroplasty.

The principal method in which this chapter will explore ALBC effects on renal function will be through a retrospective review and interrupted time series (ITS) analysis of people undergoing cemented hemiarthroplasties in a single NHS healthcare foundation trust. Chapter one has explored the background of the use of ALBC and the justification for antibiotic use within the arthroplasty population to reduce surgical site infection (SSI). In this chapter, the best available evidence on the use of ALBC and gentamicin and its effects on renal function will also be explored with inferences made to the trauma population.

The focus of this chapter is the analysis of a database of prospectively collected data from patients at the Northumbria Healthcare NHS Foundation Trust (NHCT) over a 10-year period. Observational techniques including interrupted time series (ITS) analysis are used to investigate the rates of acute kidney injury (AKI) in patients receiving cemented hemiarthroplasties. The aim being to determine whether different ALBC or different systemic (intravenous) doses of gentamicin have had any effects on the rate of renal dysfunction.

The discussion of the results of the analyses includes the strengths and weaknesses of this study and identify recommendations for future areas of investigation.

2.2.1 Hip hemiarthroplasty population

When considering the use of ALBC as prophylaxis in hemiarthroplasty for fracture neck of femur, there is a paucity of studies on its effect on renal function especially in conjunction with intravenous (IV) gentamicin administration. I have therefore in chapter one used the elective joint replacement population to discuss the evidence for the relationship between gentamicin prophylaxis and AKI. This population is the closest group comparable to the trauma hip hemiarthroplasty population, however, there are much higher rates of AKI in the hip fracture population with the evidence explored below.

The cohort who experiences hip fractures tend to be frail, elderly and are patients with numerous comorbidities at a higher risk of mortality. The reported mortality rate at one month following a hip fracture is 7% and increases to 30% by one year (Boulton, Johansen, and Wakeman 2016). The risk of AKI has also been described to be significant in patients who have a hip fracture. An observational cohort of 2848 consecutive hip fractures at Nottingham University Hospitals NHS Trust (NUH) reported AKI occurs in 24% of the hip fracture population with significant predictors including male gender (OR 1.48; 95% CI: 1.21 to 1.80), premorbid chronic kidney disease stage 3B or worse (OR 1.52; 95% CI: 1.19 to 1.93), age (OR 3.4; 95% CI: 2.29 to 5.2 for >85 years) and greater than one major co-morbidity (OR 1.61; 95% CI: 1.34 to 1.93). The presence of AKI during their hospital stay was also associated with a significantly increased 30-day mortality rate (no AKI 6.4% vs AKI 19.1%) and length of stay (no AKI: 15 days (IQR 11 to 23) vs AKI: 19.1 days (IQR 13 to 31)) (Porter et al. 2017).

A retrospective review of the national hip fracture database (NHFD) analysed 41,770 patients who had undergone hip hemiarthroplasties from the English Hospital Episode statistics (HES) database. They found that although patients greater than 85 years old had lower incidence of major chronic disease, they were at significantly higher risk of lower respiratory tract infection (OR=1.58; 95% CI 1.50 to 1.67), myocardial infarction (OR = 1.67; 95% CI: 1.52 to 1.83) and acute renal failure (OR = 1.54; 95% CI: 1.40 to 1.70) within 30 days of surgery (Jameson et al. 2012). Pedersen et al studied medical databases in Northern Denmark to identify 13,529 hip fractures (intracapsular and extracapsular) and found an acute renal failure (ARF) rate of 12.7% within five days of surgery and higher mortality at one year (AKI 25%, No AKI 18.3%: OR 1.3; 95% CI: 1.2 to 1.5) (A. B. Pedersen et al. 2016).

These studies show that the hip fracture population are an “at risk” group for developing AKI and is an important consideration when altering any aspect of their perioperative care that may effect renal function. Aminoglycosides such as gentamicin administered systemically and/or via ALBC may

increase the AKI risk that this cohort of patients is exposed to. The increased exposure to gentamicin via high dose ALBC a participant in the WHiTE 8 trial may be exposed to is discussed below.

2.2.2 Gentamicin exposure in the WHiTE 8 trial

The low dose single ALBC used in the WHiTE 8 trial is Palacos R+G which contains radio-opaque cement with 0.5g of gentamicin in each 40g packet. The high dose dual ALBC used is COPAL G+C and contains 1g of gentamicin and 1g of clindamycin in each 40g packet. Systemic antibiotics are the standard of care for hip fractures so we anticipated that these would be used across all the trial sites however there is no "ideal" antibiotic guidance (British Orthopaedic Association 1953). The pragmatic nature of this trial meant that other factors such as implant choice and choice of prophylactic intravenous antibiotics were left to the discretion of the recruiting sites surgical team. Many hospital sites including NHCT used gentamicin as part of their intravenous protocol for SSI prophylaxis hence the potential for concern on AKI explored in this chapter.

An initial prospective quasi-randomised controlled trial conducted at NHCT on 848 hip fracture patients showed a statistically significant reduction in the deep infection rate (3.5% to 1.1%) with no significant difference in complication rates including renal failure at 30 days (Sprowson et al. 2016). During this trial there was a decrease in the intravenous dose of gentamicin used from 4.5mg/kg to 3mg/kg which could have acted as a confounding variable in the study results but may have also had a protective effect on risk of AKI.

Here we further explore the in vitro antibiotic elution profile of each of these cements, which is graphically represented below in figure 1 (Kuehn, Ege, and Gopp 2005). As shown, the antibiotic gentamicin released from Copal G+C is significantly higher than that of Palacos R+G at each time point with release plateauing at day five. This to a degree is expected, as there is double the dose of gentamicin in the Copal G+C versus Palacos R+G. However, the dose released from these in vitro samples is more than double at each time point beyond day 2 and this is thought to occur due to the modified elution characteristics that occur from the addition of clindamycin to the Copal G+C cement (Walenkamp and Argenson 2007).

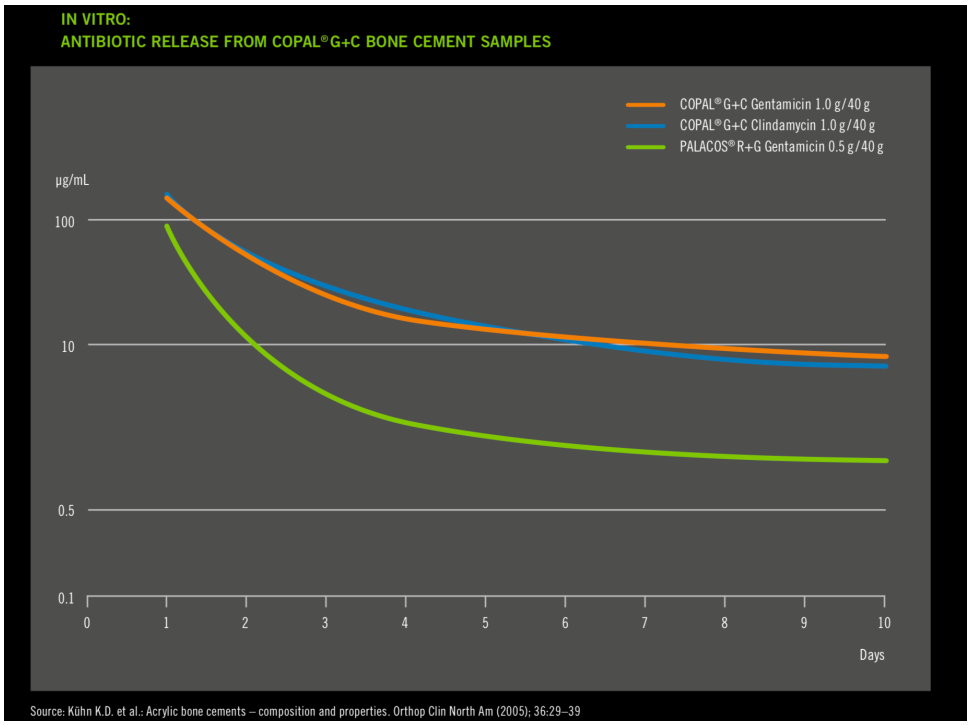


Figure 1: In vitro antibiotic release from Copal G+C bone cement.

*This figure was published in Kuehn, K. D., Ege, W., & Gopp, U. (2005). Acrylic bone cements: Composition and properties. In *Orthopaedic Clinics of North America* (Vol. 36, pp. 17–28). https://doi.org/10.1016/j.ocl.2004.06.010. Copyright to reproduce image 15/09/2024

Figure 2 also shows the concentration of gentamicin released from hardened bone cement between the different cement brands (Kühn 2013) in the first seven days. When comparing Copal G+C to Palacos R+G there is almost a 4 times increased release rate in the Copal G+C even though the gross concentration is only doubled.

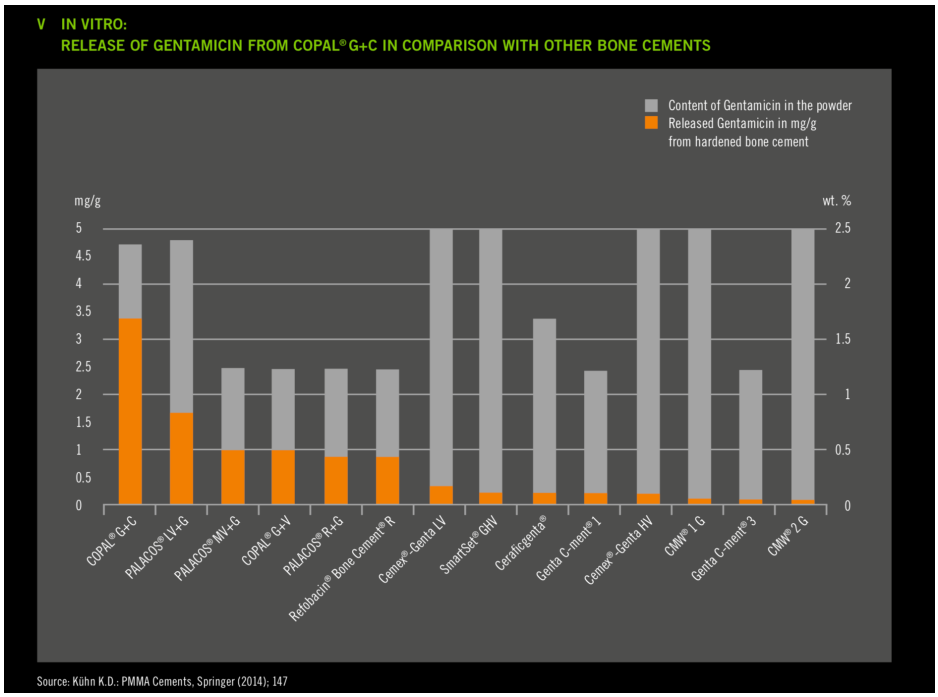


**Figure 2: In vitro release of gentamicin from Copal G+C in comparison with other bone cements*

* Published in PMMA cements (2014). (Kühn 2013) Copyright to reproduce image 16/09/2024

2.2.3 Acute renal failure definition and classifications systems

When investigating AKI as an outcome it is necessary to first define the outcome measure. Prior to 2004 there was no consensus on a definition of acute renal failure (ARF) in patients, with more than 30 different definitions being used in the literature (Bellomo et al. 2004). Drawing comparisons between studies proved difficult due to the heterogeneity in definitions. Additionally, renal dysfunction had a nomenclature change in 2002 by the Acute Dialysis Quality Initiative (ADQI) to kidney injury as this encompasses the full spectrum from mild impairment to irreversible failure of function (Mehta et al. 2007; Lewington and Sayed 2010)

In 2004 the ADQI achieved consensus on a definition now known as the RIFLE classification (Bellomo et al. 2004). This uses the serum creatinine or urine output to classify AKI into three severity categories: Risk, Injury and Failure. There are also two outcome sub types; loss, and end stage kidney disease which are classified at four weeks and three months respectively after commencing renal replacement therapy (RRT).

The RIFLE classification (table 2) can be fulfilled based on blood chemistry or urine output. A point to note is that in the category of failure the criteria can also be met through an acute rise of ≥0.5mg/dl (44μmol/l) in serum creatinine when the baseline serum creatinine is ≥4mg/dl (353μmol/l). The

classification has been extensively validated with large studies to show that increasing AKI severity as defined using RIFLE leads to increasing patient mortality (Bagshaw et al. 2008; Kellum, Bellomo, and Ronco 2007; Ricci, Cruz, and Ronco 2008; Joannidis et al. 2009; Ostermann and Chang 2007).

Further modification to the RIFLE criteria were suggested in 2007 by the Acute Kidney Injury Network (AKIN classification) to include small changes in serum creatinine 0.3mg/dl (26.5μmol/l) when they occur within a 48-hour period of measurement. The modified classification also did not require correlation to baseline values which proved advantageous in the more critically ill patient where renal function was already compromised. In 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) group again modified the classification to account for patients under the age of 18 (Khwaja 2012).

Several studies have compared the different classification systems and have shown that all three are effective in predicting mortality in patients with none or marginal differences between the classifications. Fuji et al. (Fujii et al. 2014) studied 49,518 admissions and found that RIFLE and KDIGO were equivalent in predicting AKI and mortality with AKIN being inferior. A smaller study conducted on 194 patients showed that all three classifications were good predictors of mortality with no significant difference between them (Levi et al. 2013). A meta-analysis of 171,889 patients concluded no difference in predicting hospital mortality between the RIFLE and AKIN classification in intensive care or cardiac patients (Xiong et al. 2015). Currently there is still no consensus or gold standard regarding the ideal classification system for detecting AKI and NICE does not recommend one over the other (NICE 2019).

The RIFLE classification of AKI was the outcome measure used in this study as it has been extensively validated and is feasible to retrospectively apply to the routinely collected serum creatinine data in peri-operative patients in the dataset used for this study. The major advantage of its use is that it correlates changes in serum creatinine to baseline values and thus can attribute serum creatinine changes to the intervention that may contribute to an AKI e.g., nephrotoxic antibiotics in the perioperative period.

Table 2: RIFLE classification of Acute Kidney Injury

	Glomerular Filtration Rate Criteria	**Urine Output Criteria**
Risk	Increased SCreat x1.5 or GFR decrease>25%	UO<0.5ml/kg/h x 6 hours
Injury	Increased SCreat x2 or GFR decrease>50%	UO<0.5ml/kg/h x 12 hours
Failure	Increased SCreat x3 or GFR decrease>75% Or SCreat >4mg/dl with an acute rise of 0.5mg/dl	UO<0.3ml/kg/h x 24 hours Or Anuria x 12hours
Loss	Persistent ARF = complete loss of kidney function >4 weeks	
ESKD	End Stage Kidney Disease (>3months)	

SCreat: Serum creatinine, ARF: Acute Renal Failure, GFR: Glomerular filtration rate, UO: Urine output, ESKD: End stage kidney dysfunction

2.3 Rationale and Aims

I have discussed the potential impact of ALBC on renal function using the elective population and explored the gentamicin elution profiles from the high dose ALBC Copal G+C. It has also been established that the trauma population (neck of femur fractures) are at a high risk of mortality and AKI. At the time of designing this study the WHiTE 8 trial results were unknown. If the trial had shown that a significantly greater proportion of deep infections can be reduced with Copal G+C compared to Palacos R+G, then the use of high dose dual ALBC would potentially have become routine practice in cemented hemiarthroplasties in the UK.

The current evidence for high dose dual ALBC and its effect on AKI on the patient undergoing a hemiarthroplasty have not been sufficiently investigated in the literature. Therefore, the first key aim of this chapter was to determine the relationship between low dose (Palacos R+G) and high dose (Copal G+C) and its effects on the rate of post-operative AKI. Additionally, the concurrent use of intravenous gentamicin (common practice) in addition to ALBC provides a cumulative dose in a group of a patients at higher risk of AKI. Therefore, my second aim was to determine whether changing cumulative doses of gentamicin (ALBC and intravenous) influenced the rate of post-operative AKI in the hemiarthroplasty population. The post-operative time-period of interest was five days as the local gentamicin concentrations have been shown to plateau at around day five (figure 1). Therefore, there would be only minimal cumulative dose changes from day five onwards and subsequently minimal impact on kidney function.

These aims were to therefore form additional safety advice for hospital trusts participating in the WHiTE 8 trial and ultimately for those trusts that may have chosen to change practice to high dose ALBC based on the conclusions of the trial. The results of this chapter were completed before the majority of the WHiTE 8 trial patients were recruited and so it did serve to inform practice during the trial recruitment period.

To test these aims, there are various study designs that could have been used including an RCT, national registry data or an observational dataset. Randomised controlled trials (RCTs) are considered the gold standard when evaluating the efficacy and effectiveness of health care interventions. Randomisation allows for the control of confounding variables, and with appropriate allocation concealment can minimise selection bias (Odgaard-Jensen et al. 2011; Viera and Bangdiwala 2007). However, RCTs are not always the most practical experimental design due to factors such as resources, time, and cost. The outcome of interest is post-operative AKI, which is a rare adverse event with an

incidence rate of around 5% in ALBC groups (Srisung et al. 2017). A power calculation to design a non-inferiority trial assuming a 5% AKI rate in both control and experimental groups at 90% power would require a sample size of 16,278 patients (excluding a difference of 1% in favour of the standard group) (Sealed Envelope Ltd. 2022). Firstly, the cost of this study would not be justified for the research question posed, and the length of time needed to recruit this number of patients would be the best part of a decade across 20 or more healthcare sites. Secondly, embedding this outcome as a secondary one in a trial such as the WHiTE 8 trial which has a sample size of 4920 patients would achieve a power of less than 50% thus it would be unlikely that confident conclusions could be made. Thus, a RCT design is not the most feasible method to investigate these aims.

National registries such as those used for joint arthroplasty and hip fractures in many countries such as UK, Australia and Scandinavian countries have been an invaluable source of data to change practice and to provide the large samples sizes needed to detect rare events (Hughes, Batra, and Hallstrom 2017). Unfortunately, the UK NHFD did not record cement type as a variable in its database during the timeline of this study and thus cannot be used to answer our research questions.

The method chosen to test the stated aims was analysis of a local observational dataset at NHCT. The trust routinely collects prospective data on all hip fractures to submit for NHFD data collection purposes and for internal audit. The data collected includes patient characteristics including age, gender, comorbidities, and fracture type as well as operative and post-operative outcomes including surgical method, implants used (including cement), and post-operative complications. This digitalised database of patients who had hip fractures spanning from January 2008 till August 2018 were made available to test the study aims.

The primary aims of this study are:

1. To quantify and draw inferences on the rate of AKI as classified by the RIFLE criteria within five days post-surgery in the low dose single and high dose dual ALBC groups

2. To quantify and draw inferences on the rate of AKI as classified by the RIFLE criteria within five days post-surgery with different intravenous gentamicin regimens

The secondary aims of this study are:

1. To quantify and draw inferences on the rates of admission to critical care within 30 days for AKI as classified by the RIFLE criteria for groups with different combinations of ALBC and intravenous gentamicin regimens

2. To quantify and draw inferences on the rates of 30-day-mortality for groups with different combinations of ALBC and intravenous gentamicin regimens

2.4 Northumbria Healthcare NHS Foundation Trust timeline of practice

In NHCT, patients undergoing a hemiarthroplasty have ALBC in conjunction with parenteral antibiotics preoperatively as part of their operation to protect against SSI.

The trust covers a wide geographic area and admits around 600 hip fractures per year with approximately 50% of the fractured hip population being treated with a hip hemiarthroplasty. A local database of all hip fractures and their treatments along with comorbidity and complication data has routinely been collected in this trust since 2008. During this time there have been numerous changes in both the antibiotic dose delivered thorough ALBC and in the parenteral antibiotic regimen as highlighted in Figure 3.

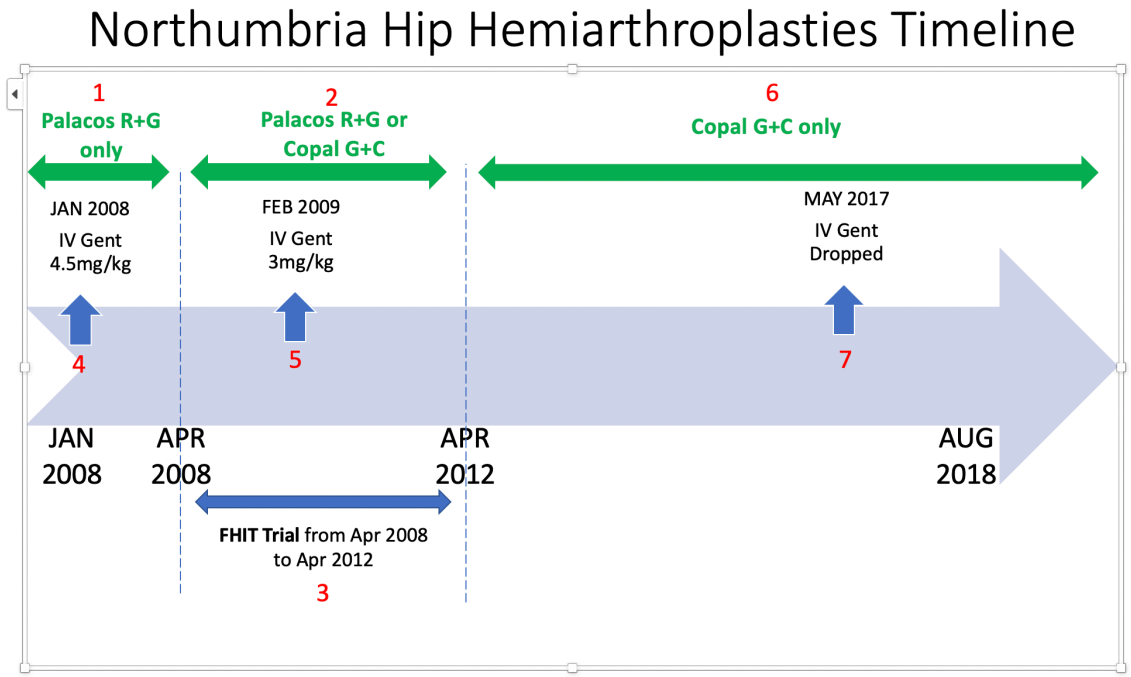


Figure 3: A timeline of intervention changes at NHCT for intravenous gentamicin and ALBC

IV: intravenous, Gent: Gentamicin, FHIT: Fracture hip infection trial.

The database starts from January 2008 and runs to the August 2018. Below are the highlighted timeline changes from figure 3:

1. During the period of January 2008 to March 2008 the only ALBC used in the trust was Palacos R+G
2. During the period of April 2008 to April 2012 patients received either Palacos R+G or Copal G+C ALBC

3. During the period of April 2008 to April 2012 the FHIT trial was conducted which was a quasi-randomised experiment comparing Palacos R+G to Copal G+C ALBC
4. At the start of the period patients received intravenous gentamicin at 4.5mg/kg preoperatively
5. In Feb 2009 the intravenous gentamicin dose dropped to 3mg/Kg preoperatively
6. During the period of May 2012 and August 2018 patients received Copal G+C ALBC
7. In May 2017 intravenous gentamicin was dropped from the preoperative antibiotic regimen

The Northumbria site was also a recruiting site for the WHiTE 8 trial and had been recruiting to this trial since September 2018 therefore a decision was made to only include data up to the commencement of the trial as not to interfere with the blinding process of the trial. This longitudinal dataset spans 10 years from 2008 to 2018. As I have shown above, there are many interventions that have taken place over the period which may have influenced the AKI rate in the population post-operatively. This poses a challenge for analysis of patients during this timeline due to differing population exposures to gentamicin in ALBC and intravenous administration. When making meaningful comparisons between groups of patients the total cumulative dose of gentamicin must be considered. The different ALBC and IV gentamicin doses in the period have created five groups with decreasing cumulative systemic doses (IV +Local) (Table 3)

Table 3: Cumulative dose relationship between ALBC and intravenous gentamicin

GROUP 1	Copal with intravenous gentamicin 4.5mg/kg	 Decreasing cumulative systemic dose of gentamicin
GROUP 2	Palacos with intravenous gentamicin 4.5mg/kg	
GROUP 3	Copal with intravenous gentamicin 3mg/kg	
GROUP 4	Palacos with intravenous gentamicin 3mg/kg	
GROUP 5	Copal with no intravenous gentamicin	

The challenge in the dataset is that there is a degree of overlap in some of the intervention changes with much smaller patient numbers available for the earlier changes. This has been

shown in figure 4. Therefore, there may be significantly different baseline patient characteristics and insufficient power between the groups causing imprecision in my analysis.

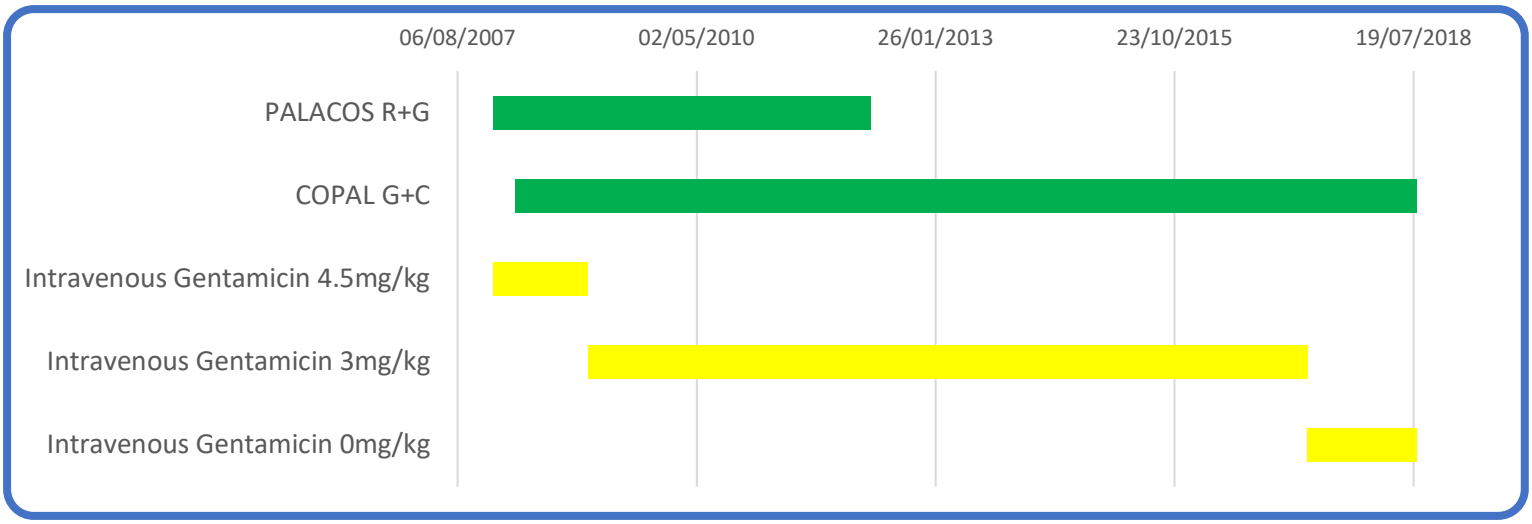


Figure 4: GANTT chart of antibiotic related interventions at NHCT

2.4.1 Observational analysis techniques

Observational techniques (non-experimental) can be used to analyse this data such as before-and-after design but must be used with caution due to the threat to internal validity. I could compare ALBC types using the Chi squared test and analyse the underlying baseline patient characteristics to guide our results. The Cochran-Armitage test (chi squared test for trend) could also be used to compare the different intravenous gentamicin groups. These simple tests can provide some initial results quickly from the interventions investigated before applying further statistical techniques to complement the evidence.

Threats to internal validity are alternative explanations for causality and can be due a variety of factors including the Hawthorne effect, regression to the mean and validity of the outcome measure over time. The Hawthorne effect is where participants modify their behaviour in response to awareness of being observed (Kontopantelis et al. 2015). Regression to the mean is a mathematical phenomenon where random variations in repeated data i.e. extreme highs and lows can be followed by repeated measurements closer to the mean (Morton and Torgerson 2005). Thus, this needs to be considered otherwise incorrect inferences on causality may be made. During the study timeline the outcome measure (RIFLE criteria) is still valid and as this data is retrospectively collected at the end of the observed period, so the Hawthorne effect is not applicable. However, regression to the mean is a real threat to internal validity especially with unbalanced groups with small numbers where extreme

values can potentially have the unintended consequence of skewing the dataset. A solution to rectify this is by using either quasi-experimental or experimental design.

Experimental design (e.g., a RCT) is not an option as discussed above but quasi-experimental designs can be used to complement the analysis. A quasi-experimental study looks at the relationship between an intervention and its target population before and post intervention without the element of randomisation (Harris et al. 2006). An interrupted time series (ITS) design (a quasi-experimental subtype) to analyse the dataset to complement the observational techniques discussed above.

2.4.2 Interrupted time series

An interrupted time series (ITS) analysis can evaluate the effect of an intervention on a longitudinal dataset through regression modelling. This is a quasi-experimental design as it allows analysis of observational data, where randomisation has not occurred, and can account for pre-intervention trends within the longitudinal dataset (Kontopantelis et al. 2015; Zhang, Wagner, and Ross-Degnan 2011). This method is often used in "natural experiments" in settings where data are routinely collected, but where it is not feasible to evaluate interventions using an RCT design. There are numerous studies using the technique in the medical literature including financial incentives to improve blood glucose monitoring, use of a digital application to improve compliance to antibiotic stewardship policy and personal electronic devices to improve self-monitoring adherence in a paediatric weight management programme (Raiff and Dallery 2010; Charani et al. 2017; Cushing, Jensen, and Steele 2011).

The components of an ITS model are the pre-intervention slope, the level change at the time of intervention and the level change between pre-and-post intervention. To satisfactorily use this design, we must have a clearly defined period at which the intervention occurred to differentiate the pre-and-post intervention period. ITS also works best with outcomes that occur in the short term after an intervention is initiated, rather than an effect that occurs over a variable time period (Kontopantelis et al. 2015; Bernal, Cummins, and Gasparrini 2017). The ITS model is appropriate to use for the AKI dataset for this study due to the long timeline of data collection and the immediate change that occurs after an intervention (antibiotic concentration) change.

Regression modelling can be linear, logistic or Poisson depending on the nature of the outcome variable. Linear and logistic regression modelling is used for a continuous and categorical outcome

data respectively. Poisson regression modelling is used when the outcome variable is a count, and this method is used elsewhere in this thesis (Chapter three – Factorial trial).

In order to use the ITS method there are three basic assumptions that need to be made about the observational dataset (Penfold and Zhang 2013; Bernal, Cummins, and Gasparrini 2017; Kontopantelis et al. 2015). Firstly, we need to assume that the pre-intervention trend is linear and there needs to be enough pre-intervention data points (minimum 6 points) to both visually and statistically confirm this. Secondly, the ITS model assumes that the population characteristics remain constant throughout the time investigated. It is important to ensure that this assumption is valid prior to analysis so any change in outcome can be attributed to the intervention only. Thirdly, if an outcome occurs due to a factor other than the intervention, there is no comparator against which to adjust the results. This means that before selecting the ITS method we must be sure that there are no other factors during the study period that may have contributed to the outcome other than the intervention investigated.

Prior to starting the analysis, the timeline for the dataset at NHCT was inspected to determine whether an ITS analysis was an appropriate option. Data was available in sufficient quantity to satisfy the first assumption. The population involved in the intervention changes were unchanged i.e., fracture neck of femur patients and hence there was no reason to believe that the population characteristics would have changed in the 10-year period either, satisfying the second assumption. There were no apparent factors that could have changed the outcome of renal function from the immediate surgical management of hip fractures other than the interventions being investigated thus the third assumption was satisfied.

The effect of the intervention can take different forms. There can be a change in the gradient (sustained effect), level (immediate effect) or both and this may occur acutely or change with a period of lag. Some possible impact models are illustrated in Figure 5.

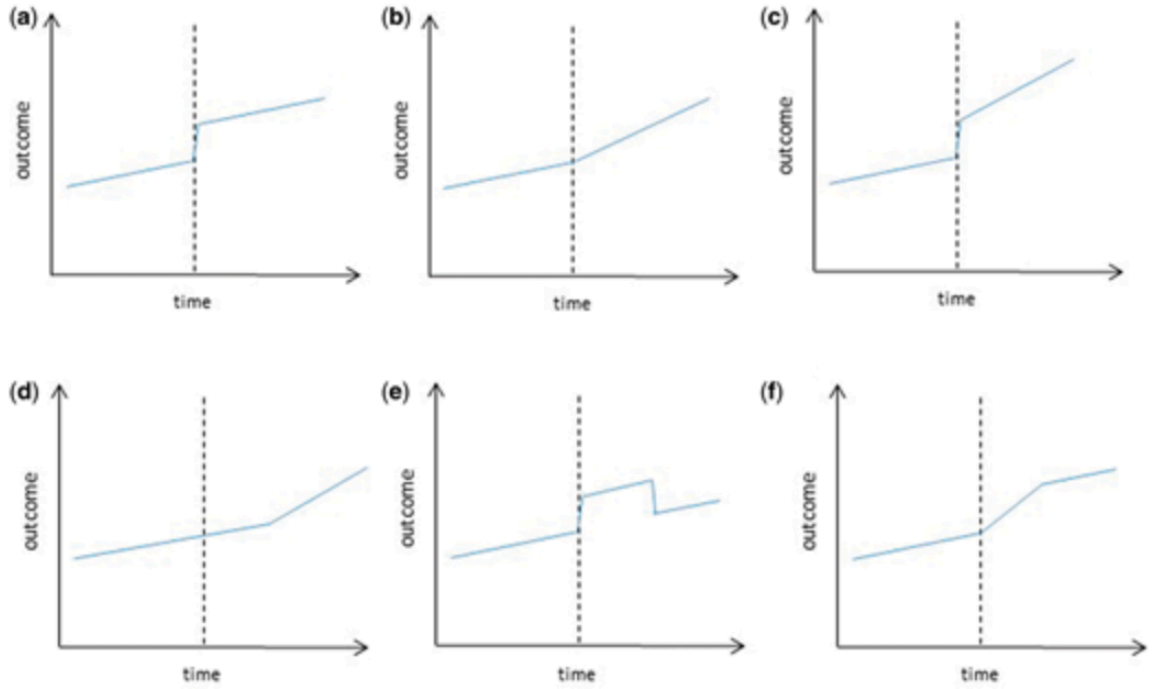


Figure 5: Examples of impact models used in ITS (Bernal, Cummins, and Gasparrini 2017)

(a) Level change
(b) Slope change
(c) Level and slope change
(d) Slope change with a lag
(e) Temporary level change
(f) Temporary slope changes leading to a level change

The statistical power of an ITS is dependent on a multitude of factors including confounders, distribution of data points and effect strength. Zhang et al (2011) conducted numerous simulation-based power calculations and concluded that power increased with increased number of time points, decreased autocorrelation and increased effect size (Zhang, Wagner, and Ross-Degnan 2011). Unbalanced designs i.e., where there are a different number of time points before and after the intervention also resulted in decreased power; however, in routine data sets, this is a factor which is hard to control. An important strength of ITS over other observational designs such as before-and-after is the ability to analyse the data pre- and post-intervention accounting for pre-intervention trend. This ensures that any statistically significant change can be more confidently attributed to the intervention applied to the population thus creating more robust conclusions (Penfold and Zhang 2013).

The dataset that this ITS design is applied to has challenges that prevent this from being a simple analysis due to the interaction between ALBC and Intravenous gentamicin. The series of interventions i.e., change in ALBC and doses of intravenous gentamicin cannot all be represented on one ITS model due to the overlap in interventions during time period 3 in figure 3. Therefore, two models will be created to allow comparison between cement types whilst considering the intravenous dose confounder. A third model will be created comparing intravenous gentamicin dose independently of cement type if the results of the first comparison show that cement type is statistically not significant. Further details regarding the proposed models are described below.

2.4.3 Proposed ITS Impact Models:

The suggested impact models for the interventions that have occurred over the ten-year period has been visually represented below in figures 6, 7 and 8.

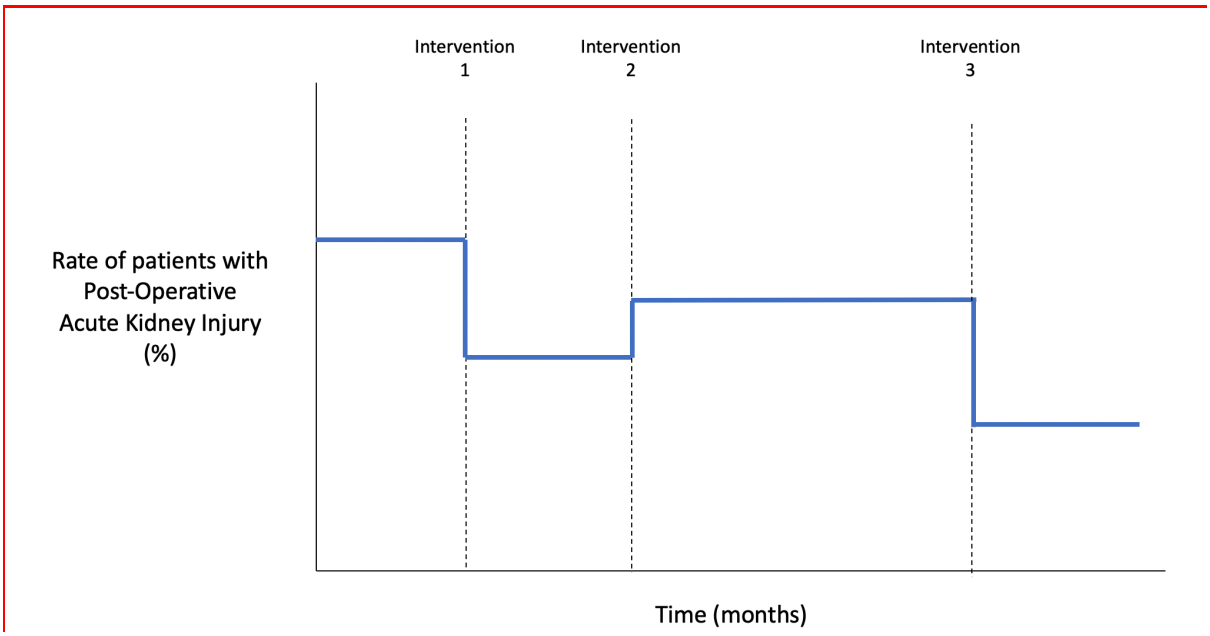


Figure 6: Model 1 - The use of Palacos + 4.5mg/kg IV gentamicin, Palacos + 3mg/kg IV gentamicin, Copal + 3mg/kg, and Copal + 0mg/kg IV gentamicin

In figure 6 at the start of the period all patients were receiving Palacos R+G cement + 4.5mg/kg IV gentamicin cement. Intervention 1 was the reduction of IV gentamicin to 3mg/kg and if there was a relationship before and after the intervention, we would expect a level change downwards due to the overall decreased combined dose of gentamicin. Intervention 2 was the change in ALBC to Copal G+C therefore increasing the combined dose of gentamicin. Therefore, a level change upward would be

predicted if a relationship existed before and after this intervention. Lastly intervention 3 was the removal of IV gentamicin and thus this significant reduction in exposure to gentamicin would be a predicted drop in level for the rates of AKI.

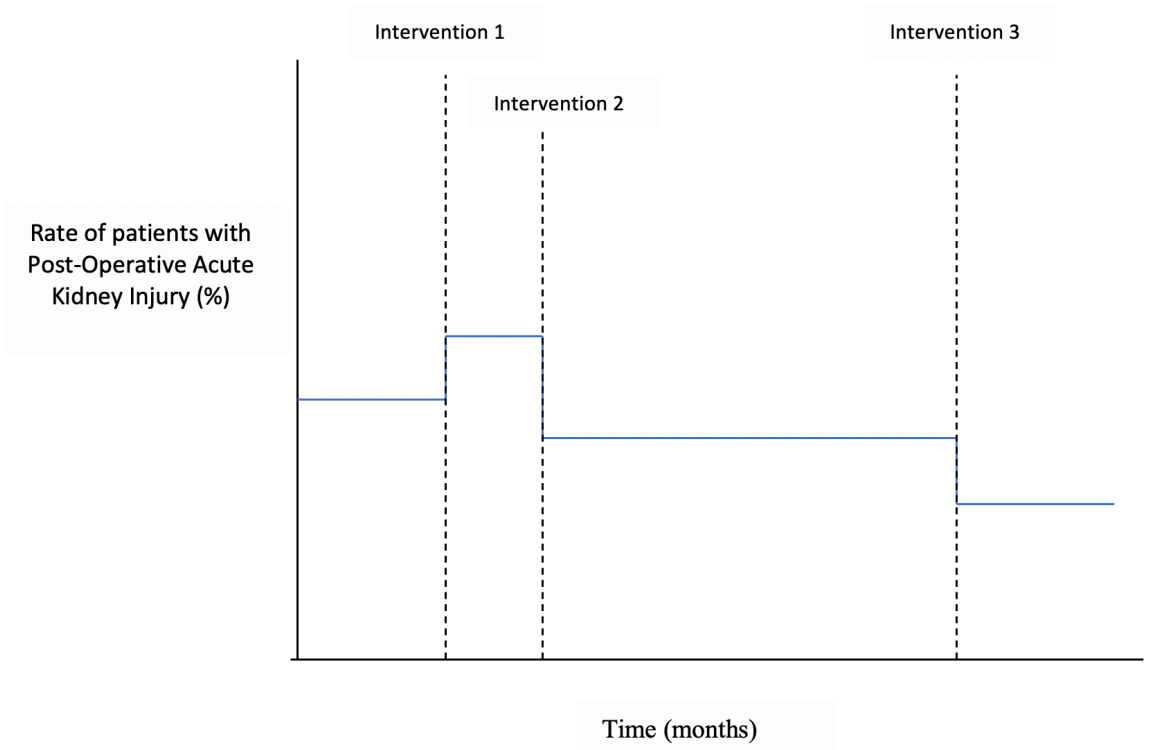


Figure 7: Model 2 - The use of Palacos + 4.5mg/kg IV gentamicin, Copal + 4.5mg/kg IV gentamicin, Copal + 3mg/kg IV gentamicin, and Copal + 0mg/kg IV gentamicin

In figure 7 at the start of the period all patients were receiving Palacos + IV gentamicin at 4.5mg/kg. Intervention 1 was the change in ALBC to Copal G+C thus resulting in a cumulative higher dose of gentamicin. A level change upwards would be expected if a relationship before and after the intervention existed. Intervention 2 was the reduction of IV gentamicin to 3mg/kg and if there was a relationship before and after the intervention, we would expect a level change downwards due to the overall decreased combined dose of gentamicin. Intervention 3 was where the intravenous gentamicin was dropped from the pre-operative regimen. We expect a downward level change from this intervention due to the expectation of a reduced rate of AKIs related to the reduced combined patient exposure to gentamicin.

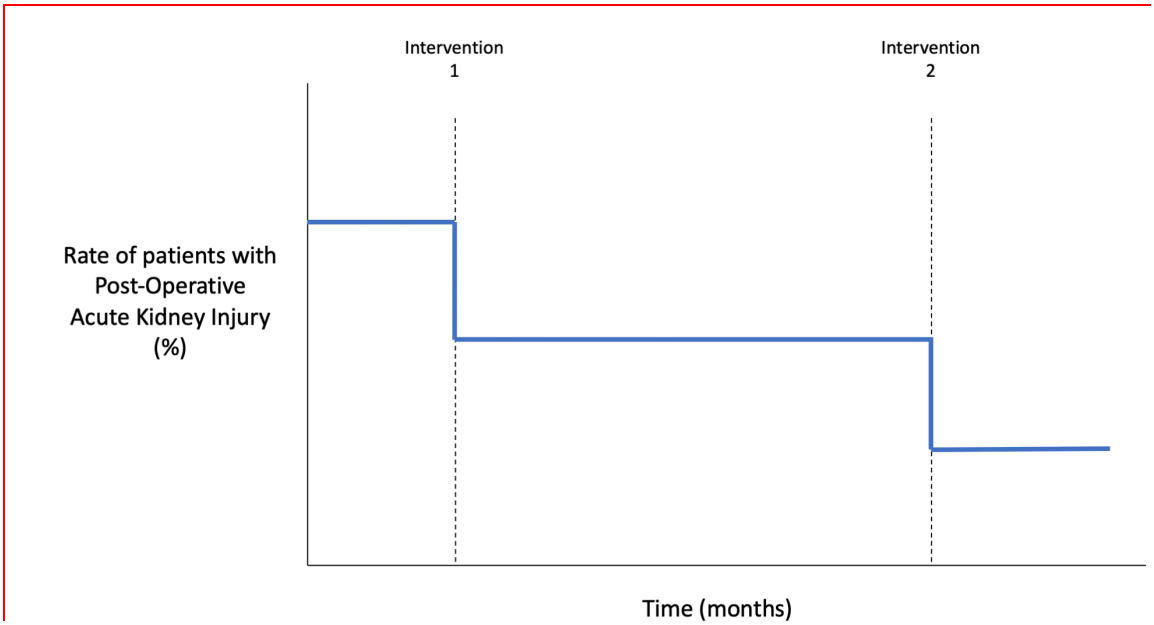


Figure 8: Model 3 - The use of 4.5mg/kg IV gentamicin, 3mg/kg IV gentamicin, and 0mg/kg IV gentamicin

In figure 8 this third model will only be used if figure 6 and figure 7 show that there is no relationship between ALBC and rate of AKI. At the start of the period all patients were receiving 4.5mg/kg of IV gentamicin with intervention 1 resulting in a drop to 3mg/kg. Intervention 2 is a completed dropout of IV gentamicin from the perioperative protocol. A level change downwards would be expected at each of these intervention points respectively due to the decreasing overall patient exposure to gentamicin. We would therefore predict a stepwise drop in rates of AKI over the total period.

2.5 Methods

2.5.1 Study Design

This was a retrospective cohort study on the incidence of AKI in hip fracture patients who received surgical treatment; a cemented hemiarthroplasty between January 2008 and August 2018. I used both non-experimental analysis (before and after comparisons) as well as a quasi-experimental (interrupted time series) analysis methodology. The data used for this study is part of a prospectively collected dataset on all hip fractures that have been treated at NHCT. The routinely collected data for each patient includes demographics (age and gender) along with operation date, operation type, cement type, comorbidities, admission to critical care unit and date of death (if applicable).

2.5.2 Inclusion Criteria

The inclusion criteria for the analyses were hip fracture patients who received surgical treatment, a cemented hemiarthroplasty. Patients who have received a hip fixation or a total hip replacement were excluded as these patients are not the population of interest in the WHiTE 8 trial. Patients who had end stage renal dysfunction already receiving renal replacement therapy were also excluded as blood tests measuring renal function are not clinically relevant for this group.

2.5.3 Outcome measure

The diagnosis of AKI is based on the RIFLE classification. This is a validated means of categorising AKI and is more suitable in this dataset than the AKIN and KDIGO modifications as there is no sub classification within 48hours for the RIFLE criteria. Post-operative measures of renal function at NHCT are usually done at day one and if normal may be repeated at some point between day three and five. Therefore, by using the AKIN or KDIGO classification we would have had most observations with missing data due to measurements not usually being taken at day 2 (48 hours). Additionally, using the RIFLE classification allowed me to use preoperative creatinine as a baseline to compare with postoperative changes thus interpreting any changes to creatinine as direct factors from the time of the operation.

The primary outcome was AKI as classified by RIFLE criteria within the first five days post operatively as an inpatient. The secondary outcome of admission to critical care was also assessed at 30 days and the endpoint for mortality was 30 days as this is routinely collected data.

2.5.4 Data collection

Northumbria Health Care Trust Caldicott permission was sought for utilisation of anonymised data for the purpose of this study. After permissions were confirmed two Microsoft Excel spreadsheets (Version 16.27) were sent via internal email by the data guardian. Spreadsheet one contained the data set of all patients who received cemented hemiarthroplasties between January 2008 and August 2018. Spreadsheet two contained the creatine results in the study period for available hip fracture population in question from their time of admission to 7 days post-operatively in listwise fashion. This information had been exported from the Trust's digital record of pathology results by the data guardian for the hip fracture database.

Spreadsheet one was arranged chronologically with regards to date of operation and each patient was given a study ID number so that an anonymised study Microsoft Excel (version 16.27) spreadsheet could be created. All relevant baseline characteristics (demographics and comorbidities) and investigated variables were extracted from spreadsheet one and two and recorded on the anonymised spreadsheet. The investigated variables collected included cement type, IV gentamicin dose, date of operation, immediate preoperative creatinine result, maximum creatine result recorded within day five, critical care admission and date of death.

I quality assured the data in the first 100 cases on spreadsheet 2 by comparing to pathology records and showed that there was 100% concordance between documented creatine values between the two resources.

There were two problems with this methodology that resulted in a manual search of the pathology database for clarification of information for several patients. The first problem was that spreadsheet two only recorded the date of blood result along with the creatine result itself. Therefore, when a patient was admitted overnight and had surgery on the same day it was not clear from spreadsheet two whether the recorded blood was before or after surgery on the same day. The pathology database also records the time of the blood test which provided clarification and was thus utilised for the cases where this problem occurred. The second problem was that spreadsheet two did not include the creatine data for all patients in spreadsheet one therefore I conducted a manual search of creatine using the pathology database was used where blood results were missing.

Intravenous gentamicin doses were not retrieved on a case-by-case basis. The assumption was that all patients received the departmental protocol dose between the time periods specified for each dose

of intravenous gentamicin i.e., 4.5mg/kg until February 2009, 3mg/kg from February 2009 to May 2017 and no intravenous gentamicin thereafter. Compliance with antibiotic protocols would only be able to be assessed if individual health records were retrieved. Pragmatically, with off-site storage of records, the resources needed, and time to conduct this, I decided against assessing this.

2.5.5 Sample Size

Sample size was determined by the number of cases that met the inclusion criteria between January 2008 and August 2018 and no formal power calculation was necessary in this study design. In the ITS analysis, I used monthly time points as the investigated period and hence observations within each period were aggregated to determine an AKI rate for analysis.

2.5.6 Statistical software

All analyses are carried using appropriate validated statistical software. Software used include STATA IC version 15 and SPSS version 24.

2.5.7 Missing Data

Despite using the methodology described for data collection, there were still instances where all creatine values, or pre-operative results were missing for cases. Missing data is traditionally categorised as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). MCAR occurs when the missing data is independent of observed and unobserved events. MAR occurs when missing data is systematically related to the observed data whilst MNAR occurs when missing data is systematically related to the unobserved data (Mack, Su, and Westreich 2018). The choice of analytical methodology e.g. complete case analysis, single or multiple imputation is dependent on the classification of the missing data.(Alma B. Pedersen et al. 2017).

For my dataset the probability of data for each patient being missing was identical with no dependency on the observed variable. The reason for the missing blood data was most likely failure of software uploading the blood result to the digital database as opposed to no bloods being taken for the patient. Hence the missing data is classed as MCAR and listwise deletion (complete case analysis) would be the appropriate analytical methodology and was thus used accordingly.

2.5.8 Non-experimental data analysis

Initial summary statistics (e.g., means and variances, or proportions and percentages) were presented showing the different proportions of patients in each group and their associated baseline

characteristics and comorbidities. The number and proportion of missing data and reasons for exclusion from final analysis were also presented.

Baseline data has been summarised to check comparability between different groups, and to highlight any difference in characteristics that could confound results. Formal statistical tests including Chi Squared test, Fischer exact test, unpaired t test, one-way ANOVA, Cochran-Armitage test, and logistic regression have been used for between group analyses as described in the results section.

Through the Cochran-Armitage test for trend, the association between a nominal variable e.g., AKI or No AKI and an ordinal variable e.g., High dose, low dose, or no dose of IV gentamicin can be tested. The null hypothesis was that there is no linear trend change in AKI rate between differing doses of gentamicin whilst the alternate hypothesis is that there will be a linear change in trend in AKI rate as the dose of IV gentamicin changes. A contingency table has been created with 2 rows for the binary variable of presence of AKI or not and 3 columns for the ordinal variables of 0mg/kg, 3mg/kg and 4.5mg/kg of IV gentamicin administration. The number and percentages for each AKI category are reported and tested at the 5% significance level to either confirm or refute the null hypothesis.

I have used the above statistical tests to compare

- AKI Rate between ALBC type (Palacos R+G vs Copal G+C)
- AKI rate between ALBC + IV gentamicin subgroups
- Trend test between AKI and IV gentamicin dose
- Rate of Critical Care admission between ALBC groups and subgroups
- Rate of Critical Care admission between ALBC groups and subgroups
- Predictive factors that determine risk of AKI, critical care admission and 30-day-mortality presented as odds ratio with 95% confidence intervals

2.5.9 Interrupted time series analysis

The first output of this analysis is a scatter plot of the time series against the mean monthly rate of renal dysfunction. The scatter plot is used to visually inspect the underlying trend and any seasonal patterns or outliers.

Segmental Regression analysis is a statistical method of estimating an intervention's effect in an interrupted time series and is used for the analysis of this study (Wagner et al. 2002). The ITS analysis was conducted using the ITSA package in STATA IC Version 15 (Linden 2015).

The interventions for each ITS analysis had been defined for the period of the study with clear differentiation between pre and post intervention periods earlier in this chapter.

The outcome is the mean number of incidences of AKI in one month as defined by the RIFLE classification. The RIFLE classification outcome counts for patients within each time point are aggregated and thus identifies the overall mean number of patients with AKI (all subtypes) at each time point. A segmented regression model was created for each ITS analysis and a change in trend (gradient) and level (intercept) of the model was tested at the time point when there was a change in antibiotic dose and/or ALBC type depending on the ITS analysis in question.

There are many medical conditions that present in increased frequency during winter seasons including cardiovascular, infectious and respiratory disorders (Ogawa et al. 2007; Mongardon et al. 2012; Fisman 2007). Evidence suggests the same may hold true with respect to AKI due to the aforementioned associated disorders that have "winter peaks" (Iwagami et al. 2018; Lombardi et al. 2021). In order to test for and subsequently adjust for seasonal fluctuation, i.e., more episodes of AKI in winter months, a seasonality variable was created for the winter months (December, January, and February). A segmented regression model was then created including the seasonality variable and again the time point for intervention change was tested for a trend or level change.

The assumption of the model created is that all observations are independent of each other but in time series data this is often violated with consecutive observations being closer together than observations that are further apart. This phenomenon known as autocorrelation can be examined by testing the regression models against lagged values of our dependent variable (presence of AKI). The Cumby-Huizinga general (Breusch-Godfrey) test was used for this analysis and was tested up to a lag of 12.

2.6 Results – Before and after analysis

2.6.1 Summary and missing data

A total of 3178 patients were identified from the database in spreadsheet 1 between 1st January 2008 and 1st August 2018. Through the methodology of data collection described, I was able to collect a complete renal dataset on 3129 patients that fit the inclusion criteria.

There were 49 cases that were excluded from the final analysis: four because the patient had received dialysis and thus did not fit inclusion criteria and 45 cases with missing creatine blood tests despite searching on the pathology database.

Table 4: Distribution of missing data from 2008-2018

Year	*No. Cases*	*Missing*	*%Missing*
2008	216	7	3.24
2009	263	5	1.90
2010	300	14	4.67
2011	312	5	1.60
2012	322	2	0.62
2013	334	5	1.50
2014	322	1	0.31
2015	303	3	0.99
2016	338	3	0.89
2017	317	0	0.00
2018	151	0	0.00
Total	3178	45	1.42

The overall incidence of missing data was low at 1.42% with less missing data occurring from 2012 onwards (Table 4).

Within this dataset of 3129 patients, 45 had missing comorbidity data (1.44%) and 45 had missing admission to critical care data (1.44%).

2.6.2 Comparison between Palacos R+G and Copal G+C groups in the rate of AKI

Using non-experimental analysis techniques, I compared the rate of AKI between those patients receiving Palacos R+G and Copal G+C irrespective of intravenous gentamicin dose. 3129 patients were used for this analysis and baseline comorbidity data for 3084 patients were available.

Statistic test: Chi Squared, unpaired t test 2 sided at 95% confidence interval.

Table 5: Baseline characteristics of ALBC groups

	PALACOS	COPAL	P value
Baseline Demographics			
No. Of Patients with data	806	2323	
Male: n, %	216 (26.8)	674 (29.0)	0.230
Female: n, %	590 (73.2)	1649 (71.0)	
Mean Age (SD)	82.2 (8.14)	82.5 (8.68)	0.351
Baseline Comorbidities			
No. of Patients with data	774	2310	
Hypertension: n, %	363 (45.0)	1238 (53.3)	0.001*
Atrial Fibrillation: n, %	168 (20.8)	532 (22.9)	0.446
IHD: n, %	113 (14.0)	443 (19.1)	0.004*
Hypothyroidism: n, %	84 (10.4)	283 (12.2)	0.298
Hyperthyroidism: n, %	8 (1)	20 (0.9)	0.670
IDDM: n, %	5 (0.6)	15 (0.6)	0.992
NIDDM: n, %	116 (14.4)	395 (17.0)	0.171
PVD: n, %	96 (11.9)	347 (14.9)	0.072
COPD: n, %	87 (10.8)	374 (16.1)	0.001*
Dementia: n, %	121 (15)	298 (12.8)	0.055
Alzheimer: n, %	75 (9.3)	300 (12.9)	0.015*

*Significant at P<0.05, Ischaemic heart disease (IHD), insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), chronic obstructive pulmonary disorder (COPD)

Table 6:Comparison of AKI according to Rifle Criteria between ALBC groups

	PALACOS	COPAL	Mean (95% CI)	P value
No. Of Patients with data	806	2323		
Clinical				
Rifle 0	764 (94.8)	2225 (95.8)	0.958 (0.95 to 0.966)	0.240
Rifle 1	28 (3.5)	73 (3.1)	0.031 (0.024 to 0.039)	0.647
Rifle 2	10 (1.2)	17 (0.7)	0.007 (0.004 to 0.011)	0.178
Rifle 3	4 (0.5)	8 (0.3)	0.003 (0.001 to 0.006)	0.548

*Significant at P<0.05

There were statistically significant different baseline comorbidities between the groups including hypertension, ischaemic heart disease (IHD), chronic obstructive pulmonary disease (COPD) and Alzheimer's. The Copal group had significantly more patients who had the above listed comorbidities but had marginally less (although not statistically significant) rates of AKI.

Further adjustment considering baseline characteristics was not undertaken as table 5 showed frailer patients in the Copal group and thus further analysis would not have shown any relevant adjustment to change the interpretation of the results.

2.6.3 Subgroup comparison of rate of AKI between ALBC groups with addition of intravenous gentamicin

Using before and after observational analysis technique I compare the rate of AKI between those patients receiving Palacos R+G and Copal G+C considering intravenous gentamicin dose. 3129 patients were used for AKI analysis and baseline comorbidity data for 3084 patients were available.

Statistic test: Chi Squared, Fisher exact test, One-way ANOVA.

Table 7: Baseline characteristics of subgroup analysis of ALBC and systemic gentamicin regimens

	PALACOS + IV Gent 4.5mg/kg	COPAL + IV Gent 4.5mg/kg	PALACOS + IV Gent 3mg/kg	COPAL + IV Gent 3mg/kg	COPAL with no IV Gent	P value
Baseline Demographics						
No. Of Patients with data	189	41	617	1938	344	
Male: n, %	47 (24.9)	10 (24.4)	168 (27.2)	541 (27.9)	123 (35.8)	0.240
Female: n, %	142 (75.1)	31 (75.6)	449 (72.8)	1397 (72.1)	221 (64.2)	
Mean Age (SD)	80.9 (8.62)	78.8 (7.40)	82.6 (7.95)	82.8 (8.47)	81.5 (9.78)	<0.001*
Baseline Comorbidities						
No. of Patients with data	185	40	589	1926	344	
Hypertension: n, %	79 (41.8)	18 (43.9)	284 (46.0)	1040 (53.7)	180 (52.3)	0.009*
Atrial Fibrillation: n, %	37 (19.6)	10 (24.4)	131 (21.2)	453 (23.4)	69 (20.1)	0.552
IHD: n, %	23 (12.2)	2 (4.9)	90 (14.6)	363 (18.7)	78 (22.7)	0.002*
Hypothyroidism: n, %	15 (7.9)	3 (7.3)	69 (11.2)	232 (12.0)	48 (14.0)	0.318
Hyperthyroidism: n, %	4 (2.1)	0 (0)	4 (0.6)	13 (0.7)	7 (2.0)	0.050*
IDDM: n, %	1 (0.5)	1 (2.4)	4 (0.6)	10 (0.5)	4 (1.2)	0.230
NIDDM: n, %	19 (10.1)	8 (19.5)	97 (15.7)	319 (16.5)	68 (19.8)	0.085
PVD: n, %	25 (13.2)	5 (12.2)	71 (11.5)	284 (14.7)	58 (16.9)	0.321
COPD: n, %	14 (7.4)	7 (7.1)	73 (11.8)	301 (15.5)	66 (19.2)	0.002*
Dementia: n, %	32 (16.9)	4 (9.8)	89 (14.4)	267 (13.8)	27 (7.8)	0.009*
Alzheimer: n, %	17 (9.0)	4 (9.8)	58 (9.4)	230 (11.9)	66 (19.2)	<0.001*

*Significant at P<0.05, IV= Intravenous, Gent = gentamicin, Ischaemic heart disease (IHD), insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), chronic obstructive pulmonary disorder (COPD).

Table 8: Comparison of AKI according to RIFLE criteria for subgroup analysis of ALBC and systemic gentamicin regimens

	PALACOS + IV Gent 4.5mg/kg	COPAL + IV Gent 4.5mg/kg	PALACOS + IV Gent 3mg/kg	COPAL + IV Gent 3mg/kg	COPAL with no IV Gent	P value
No. Of Patients	189	41	617	1938	344	
Clinical						
Rifle 0	179 (94.7)	40 (97.6)	585 (94.8)	1853 (95.6)	332 (96.5)	0.688
Rifle 1	7 (3.7)	1 (2.4)	21 (3.4)	64 (3.3)	8 (2.3)	0.876
Rifle 2	3 (1.6)	0 (0.0)	7 (1.1)	14 (0.7)	3 (0.9)	0.557
Rifle 3	0 (0.0)	0 (0.0)	4 (0.6)	7 (0.4)	1 (0.3)	0.737

*Significant at P<0.05, IV = Intravenous, Gent = gentamicin

Age, hypertension, IHD, Hyperthyroidism, COPD, Dementia and Alzheimer's all show statistically significant differences in the between group comparison. There is an increased prevalence of these diseases in the Copal population with the highest being in the group receiving Copal with no additional gentamicin intravenously. However, there is no statistically significant difference between the groups in both overall and subclassifications of the Rifle Criteria for AKI. There is a trend for the Palacos subgroups having marginally increased rates of renal dysfunction at Rifle 1 and 2 when compared to relevant Copal subgroups.

Further adjustment considering baseline characteristics was not undertaken as table 7 showed frailer patients in the Copal group and thus further analysis would not have shown any relevant adjustment to change the interpretation of the results.

2.6.5 The use of different intravenous gentamicin doses on the rate of AKI

Using the Cochran-Armitage test (Chi squared test for trend) we compare the rate of AKI between those patients receiving different intravenous gentamicin doses. 3129 patients were used for AKI analysis and baseline comorbidity data for 3084 patients were available.

Statistic test: Cochran-Armitage test, Fisher exact test, One-way ANOVA.

Table 9: Baseline characteristics of patients with different intravenous gentamicin regimens

	IV gentamicin 4.5mg/kg	**IV gentamicin 3mg/kg**	**IV gentamicin 0/kg**	**P value**
Baseline Demographics				
No. Of Patients with data	230	2555	344	
Male: n, %	57 (24.8)	710 (27.8)	123 (35.8)	
Female: n, %	173 (75.2)	1845 (72.2)	221 (64.2)	0.040*
Mean Age (SD)	80.5 (8.44)	82.7 (8.35)	81.5 (9.78)	0.001*
Baseline Comorbidities				
No. of Patients with data	225	2515	344	
Hypertension: n, %	97 (43.1)	1324 (52.6)	180 (52.3)	0.023*
Atrial Fibrillation: n, %	47 (20.9)	584 (23.2)	69 (20.0)	0.337
IHD: n, %	25 (11.1)	453 (18.0)	78 (22.7)	0.002*
Hypothyroidism: n, %	18 (8.00)	301 (12.0)	48 (14.0)	0.097
Hyperthyroidism: n, %	4 (1.78)	17 (0.68)	7 (2.03)	0.013*
IDDM: n, %	2 (0.89)	14 (0.56)	4 (1.16)	0.234
NIDDM: n, %	27 (12.0)	416 (16.5)	68 (19.8)	0.051
PVD: n, %	30 (13.3)	355 (14.1)	58 (16.9)	0.356
COPD: n, %	21 (9.33)	374 (14.9)	66 (19.2)	0.005*
Dementia: n, %	36 (16.0)	356 (14.2)	27 (7.85)	0.003*
Alzheimer: n, %	21 (9.33)	288 (11.5)	66 (19.2)	<0.001*

*Significant at P<0.05) Ischaemic heart disease (IHD), insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), chronic obstructive pulmonary disorder (COPD). IV = Intravenous.

Table 10: Comparison of AKI according to RIFLE criteria for intravenous gentamicin subgroups

	IV gentamicin dose			
	4.5mg/kg	3mg/kg	0mg/kg	P Value
No of cases of AKI (Rifle 1,2,3)				
Yes (n, %)	11 (4.78)	117 (4.58)	12 (3.49)	
No (n, %)	219 (95.22)	2438 (95.42)	332 (96.51)	0.356
Total	230	2555	344	

IV: Intravenous, AKI: Acute kidney injury.

Table 9 shows baseline differences in sex, age, hypertension, ischaemic heart disease, hyperthyroidism, COPD, dementia, and Alzheimer disease. Table 10 comparison looked at the effect of decreasing dose of IV gentamicin on the rate of acute renal failure irrespective of underlying population differences. There is no statistically significant difference between groups.

2.6.6 The rates of admission to Critical Care

Using before and after observational analysis technique we compare the rate of admission to Critical Care between those patients receiving Palacos R+G and Copal G+C and then subsequently considering intravenous gentamicin dose. 3129 patients were used for AKI analysis and baseline comorbidity data for 3084 patients were available.

Statistic test: Chi Squared

Baseline characteristics: See Table 5 and Table 7

Table 11: Critical care admission during inpatient stay between ALBC groups

	PALACOS	COPAL	P value
No. Of Patients	806	2323	
Critical Care admissions within 30 days	27 (3.3)	64 (2.8)	0.307

Table 12: Critical care admission during inpatient stay between different subgroups of ALBC and intravenous gentamicin

	PALACOS + IV Gent 4.5mg/kg	COPAL + IV Gent 4.5mg/kg	PALACOS + IV Gent 3mg/kg	COPAL + IV Gent 3mg/kg	COPAL with no IV Gent	P value
No. Of Patients	189	41	617	1938	344	
Critical Care 30 days	3 (1.6)	0 (0.0)	24 (3.9)	45 (2.3)	19 (5.5)	0.004*

*Significant at P<0.05, IV= Intravenous, Gent = gentamicin

The result of this analysis shows that there was no statistically significant difference between type of ALBC in critical care admission (p = 0.307), however, there are statistically significant differences between subgroups (p = 0.004). The highest rate of admission to critical care within 30 days was in the Copal with no IV Gentamicin group (5.5%). There was increased prevalence of comorbidities such

as hypertension, ischaemic heart disease and COPD in this group which can also result in critical care admissions.

2.6.7 The rates of 30-day-mortality for groups with different combinations of ALBC and intravenous gentamicin regimens

Using before and after observational analysis technique we compare the rate of admission to Critical Care between those patients receiving Palacos R+G and Copal G+C and then subsequently considering intravenous gentamicin dose. 3129 patients were used for AKI analysis and baseline comorbidity data for 3084 patients were available.

Statistic test: Chi Squared

Baseline characteristics: See Table 5 and Table 7

Table 13: 30-day-mortality in different ALBC groups

	PALACOS	COPAL	P value
No. Of Patients	806	2323	
Mortality 30 days	69 (8.6)	150 (6.5)	0.044*

This analysis shows a statistically significant difference in the mortality rate at 30 days between type of ALBC with an increased mortality with the Palacos R+G cement (p=0.044).

Table 14: 30-day-mortality for different combinations of ALBC and intravenous gentamicin

	PALACOS + IV Gent 4.5mg/kg	COPAL + IV Gent 4.5mg/kg	PALACOS + IV Gent 3mg/kg	COPAL + IV Gent 3mg/kg	COPAL with no IV Gent	P value
No. Of Patients	189	41	617	1938	344	
Mortality 30 days	19 (10.1)	3 (7.3)	50 (8.1)	127 (6.6)	20 (5.8)	0.264

*Significant at P<0.05, Gent = gentamicin

There are no statistically significant differences in subgroup analysis for mortality.

2.6.8 Predictive factors that determine risk of AKI, critical care admission and 30-day-mortality.

A multiple logistic regression model was created to determine the factors that predict the risk of AKI within the first five days post-operatively, 30-day-critical care admission and 30-day-mortality.

Results are presented below as odds ratio with 95% confidence intervals and P-values tested at 5% significance level.

Table 15: Predictive factors for developing AKI in patients undergoing a hip hemiarthroplasty adjusted for all variables

AKI	Odds Ratio	95% Confidence Interval		P Value
Copal ALBC	0.8	0.54	1.18	0.256
IV gentamicin	1.27	0.68	2.37	0.445
HTN	1.45	1.02	2.07	0.041*
AF	1.5	1.03	2.19	0.035*
IHD	1.14	0.74	1.76	0.538
Hypothyroid	0.73	0.4	1.33	0.3
Hyperthyroid	0.76	0.1	5.79	0.792
IDDM	2.35	0.53	10.4	0.259
NIDDM	1.04	0.66	1.64	0.864
PVD	0.84	0.51	1.41	0.517
COPD	1.65	1.08	2.53	0.02*
Dementia	0.91	0.54	1.53	0.711
Alzheimer	1.06	0.62	1.82	0.828

No. of Observation 3084

*Significant at P<0.05. Hypertension (HTN), Atrial fibrillation (AF), Ischaemic heart disease (IHD), insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), chronic obstructive pulmonary disorder (COPD). IV = Intravenous.

Hypertension (p=0.041), Atrial fibrillation (p=0.035) and COPD (p=0.02) are statistically significant predictors for acute kidney injury in this analysis. Using Copal cement is not statistically significant (p=0.256)

Table 16: Predictive factors for 30-day-critical care admission in patients undergoing a hip hemiarthroplasty adjusted for all variables

Critical Care	Odds Ratio	95% Confidence Interval		P Value
Copal ALBC	0.63	0.39	1.03	0.064
No IV gentamicin	0.41	0.23	0.71	0.002*
HTN	0.7	0.46	1.07	0.101
AF	1.11	0.67	1.82	0.687
No. of Observations	1.33	0.8	2.22	0.273
Hypothyroid	1.06	0.56	2.03	0.856
Hyperthyroid	1.95	0.43	8.72	0.384
IDDM	2.01	0.26	15.42	0.504
NIDDM	0.98	0.55	1.73	0.938
PVD	0.53	0.25	1.12	0.095
COPD	2.35	1.47	3.77	<0.001*
Dementia	0.82	0.42	1.6	0.555
Alzheimer	0.48	0.2	1.11	0.086
No. of Observations	3079			

*Significant at P<0.05. Hypertension (HTN), Atrial fibrillation (AF), Ischaemic heart disease (IHD), insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), chronic obstructive pulmonary disorder (COPD). IV = Intravenous.

The use of IV gentamicin, and having COPD are statistically significant risk factors for admission to critical care in the first 30 days of admission.

Table 17: Predictive factors for 30-day-mortality in patients undergoing a hip hemiarthroplasty adjusted for all variables.

30-day-Mortality	Odds Ratio	95% Confidence Interval		P Value
Copal ALBC	0.7	0.51	0.96	0.025*
IV gentamicin	1.14	0.7	1.87	0.598
HTN	0.68	0.51	0.91	0.009*
AF	2.22	1.66	2.98	<0.001*
IHD	1.48	1.06	2.07	0.021*
Hypothyroid	1.21	0.8	1.83	0.37
Hyperthyroid	1.37	0.39	4.75	0.624
IDDM	0.67	0.08	5.41	0.705
NIDDM	0.95	0.65	1.39	0.783
PVD	1.03	0.69	1.52	0.899
COPD	1.92	1.37	2.7	<0.001*
Dementia	1.44	1	2.09	0.05*
Alzheimer	1.04	0.67	1.61	0.873
No. of Observations	3084			

*Significant at P<0.05) Ischaemic heart disease (IHD), insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), chronic obstructive pulmonary disorder (COPD).

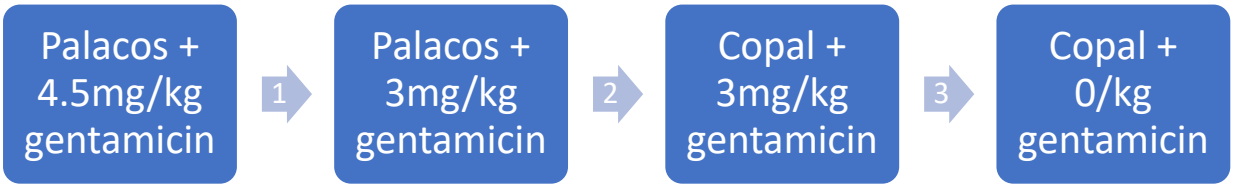
The comorbidities of hypertension, atrial fibrillation, IHD, COPD, and dementia are risk factors for 30-day mortality.

The use of Copal G+C was statistically significant in reducing 30-day mortality with an odds ratio of 0.7 (95% CI 0.51, 0.96).

2.7 Results – Interrupted time series

2.7.1 Model 1 – Combined ALBC and IV gentamicin

This model is for the changing interventions from January 2008 to August 2018 for the below interventions.



2749 patients were included in the analysis as 380 patients were excluded who received Copal G+C and 3mg/kg prior to intervention 2 during the FHIT trial.

A scatterplot of the data over the time is presented to visually inspect the trend (figure 9). Over the study timeline there is suggestion of a decreasing trend for AKI with a possibility of outliers during winter months. The interventions in the above diagram are represented by the lines 1 2 and 3 respectively.

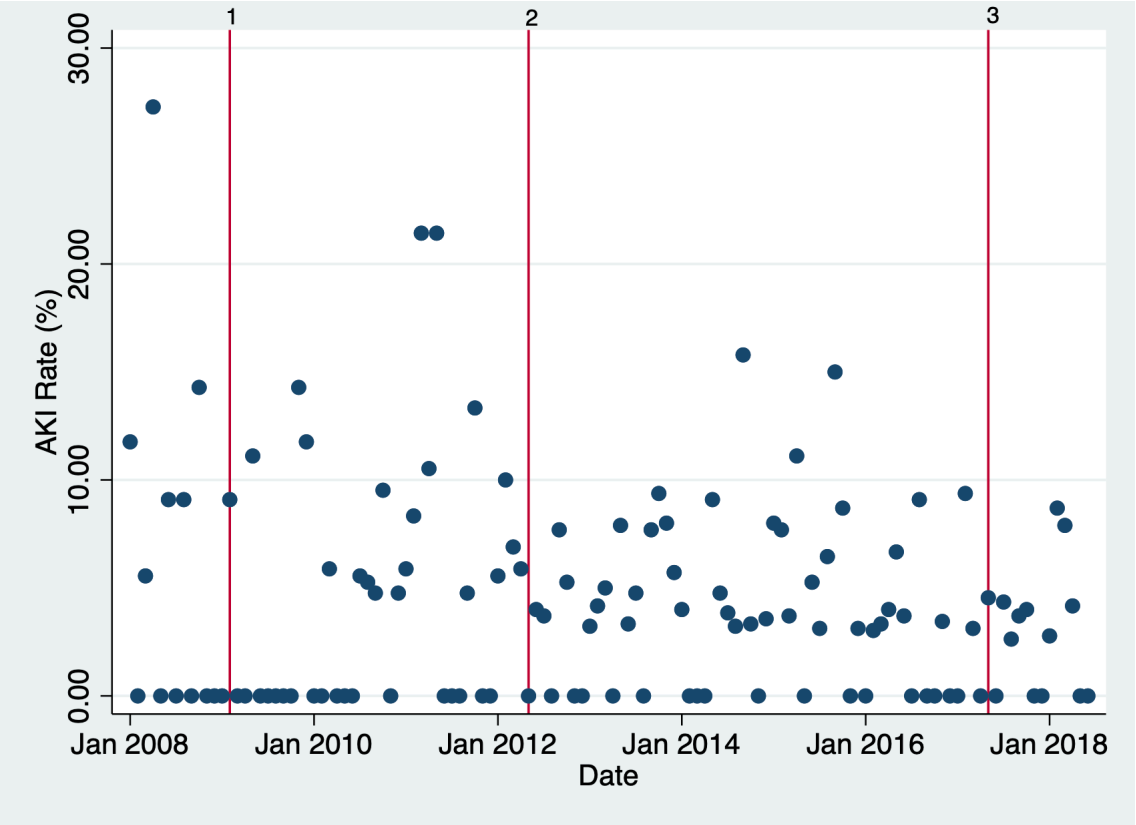


Figure 9: Scatterplot of model 1

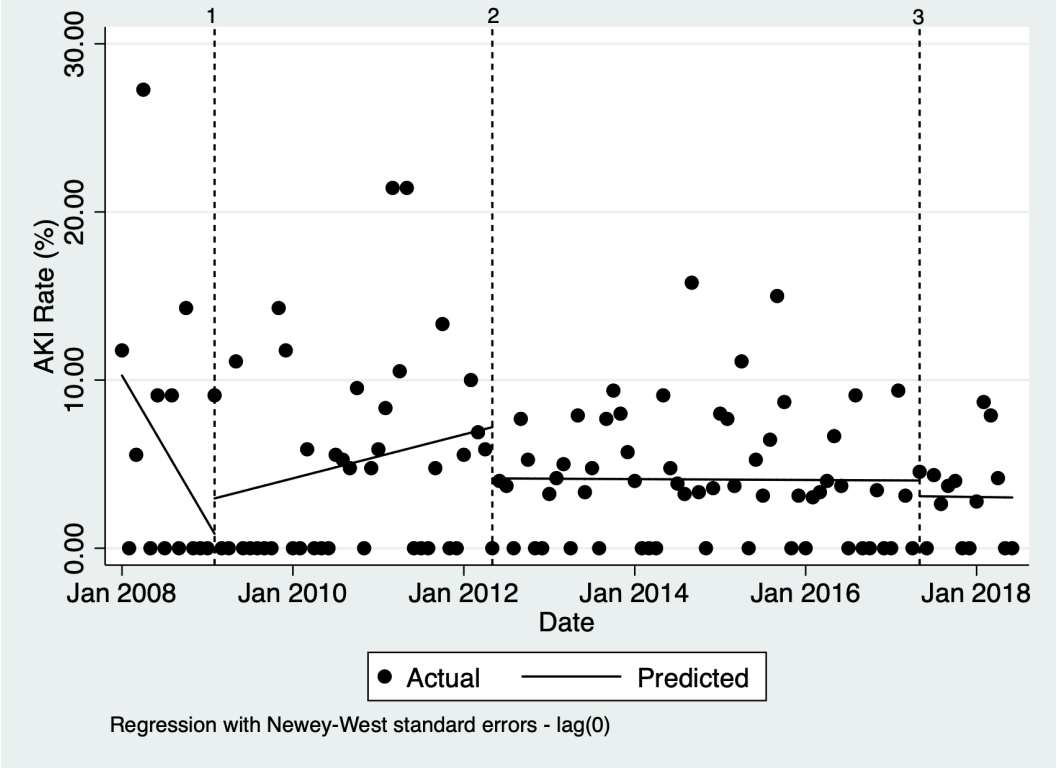


Figure 10: Unadjusted ITS of model 1

Figure 10 and Table 18 show the results of the unadjusted ITS model for seasonality. There is no level or trend changes with statistical significance at each of the three intervention changes.

Table 18: Unadjusted ITS analysis of model 1

AKI Rate (%)	Coef.	Std. Err.	P value	95% Confidence interval	
Pre-trend	-0.72	0.49	0.144	-1.70	0.25
Level change intervention 1	2.10	3.33	0.53	-4.50	8.70
Trend change intervention 1	0.83	0.50	0.097	-0.15	1.82
Level change intervention 2	-3.05	2.09	0.147	-7.19	1.09
Trend change intervention 2	-0.11	0.08	0.171	-0.27	0.05
Level change intervention 3	-0.93	1.45	0.522	-3.81	1.94
Trend change intervention 3	0.00	0.18	0.985	-0.37	0.36

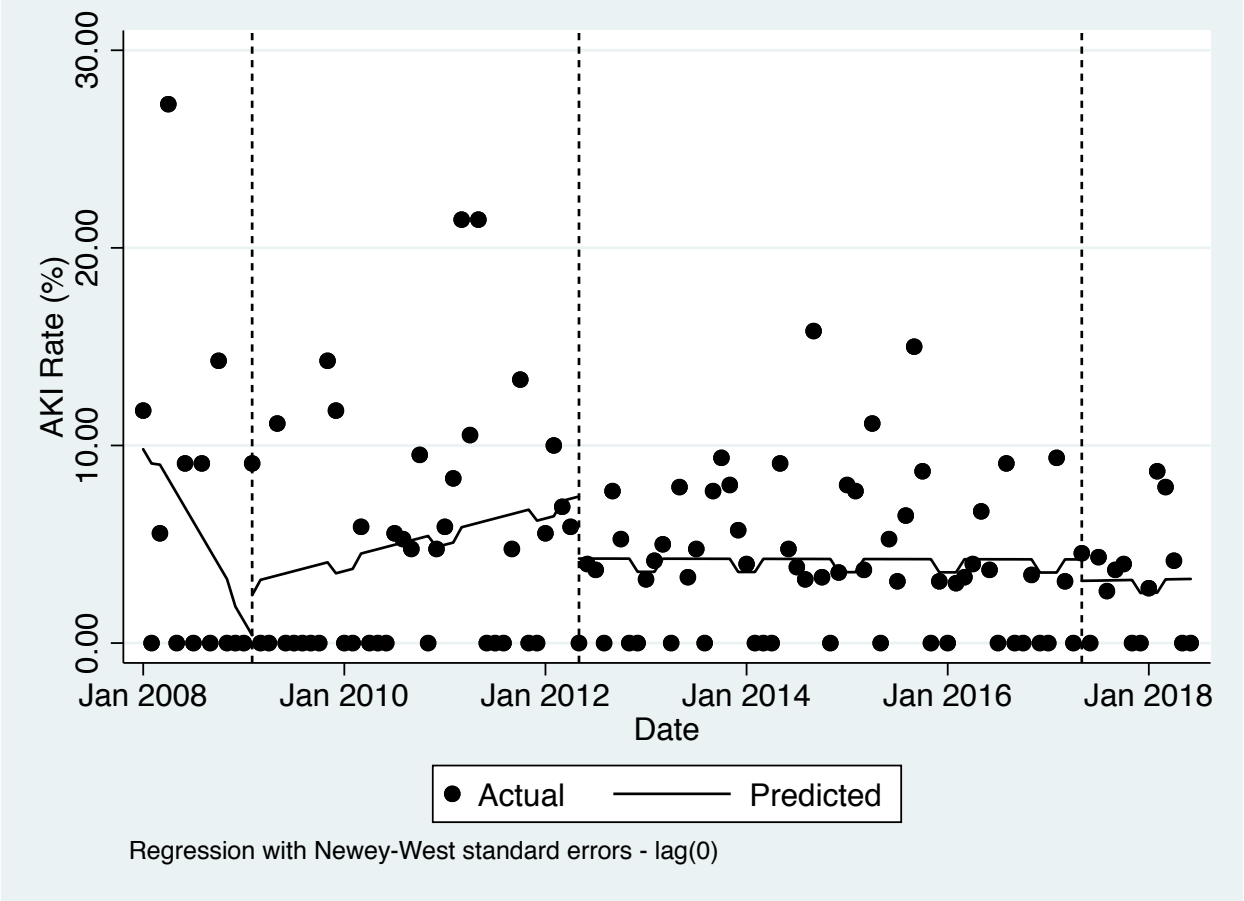


Figure 11: Adjusted ITS for seasonality

Figure 11 and Table 19 show the results of the adjusted ITS model for seasonality. There is no level or trend changes with statistical significance at each of the three intervention changes.

Table 19: Adjusted ITS analysis for seasonality

AKI Rate (%)	Coef.	Std. Err.	P value	95% Confidence interval	
Pre-trend	-0.72	0.48	0.138	-1.68	0.24
Level change intervention 1	2.02	3.32	0.544	-4.56	8.61
Trend change intervention 1	0.84	0.49	0.092	-0.14	1.81
Level change intervention 2	-3.14	2.13	0.143	-7.36	1.08
Trend change intervention 2	-0.11	0.08	0.175	-0.27	0.05
Level change intervention 3	-1.09	1.49	0.468	-4.04	1.87
Trend change intervention 3	0.01	0.19	0.966	-0.37	0.39
Season	-0.67	0.93	0.475	-2.51	1.17

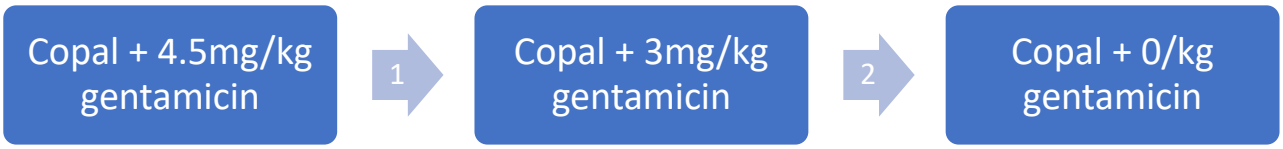
Table 20: Autocorrelation analysis of model 1

Lag	Chi2	P value
1	0.122	0.726
2	0.450	0.502
3	2.382	0.123
4	0.040	0.841
5	0.808	0.369
6	0.092	0.762
7	0.881	0.348
8	0.199	0.655
9	0.012	0.911
10	0.072	0.788
11	0.288	0.591
12	0.672	0.413

There is no statistical evidence of autocorrelation in this analysis up to a lagged value of 12 (table 20).

2.7.2 Model 2 – Copal group and IV gentamicin

This model is for the changing interventions from January 2008 to August 2018 for the below interventions.



A scatterplot of the data over the time is presented to visually inspect the trend and shows decreasing AKI rate over time (figure 12). The interventions in the above diagram are represented by the lines 1 and 2 respectively.

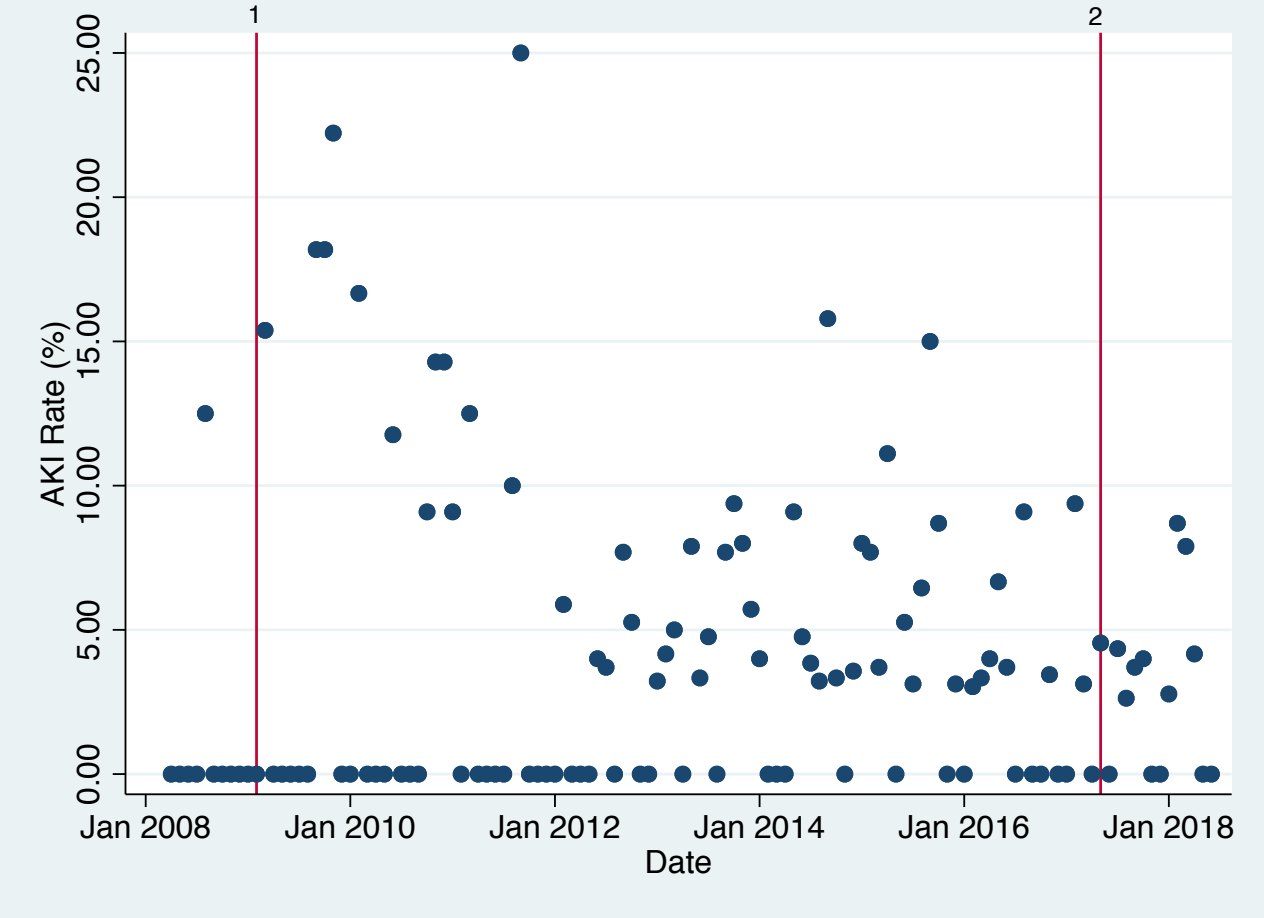


Figure 12: Scatterplot of model 2

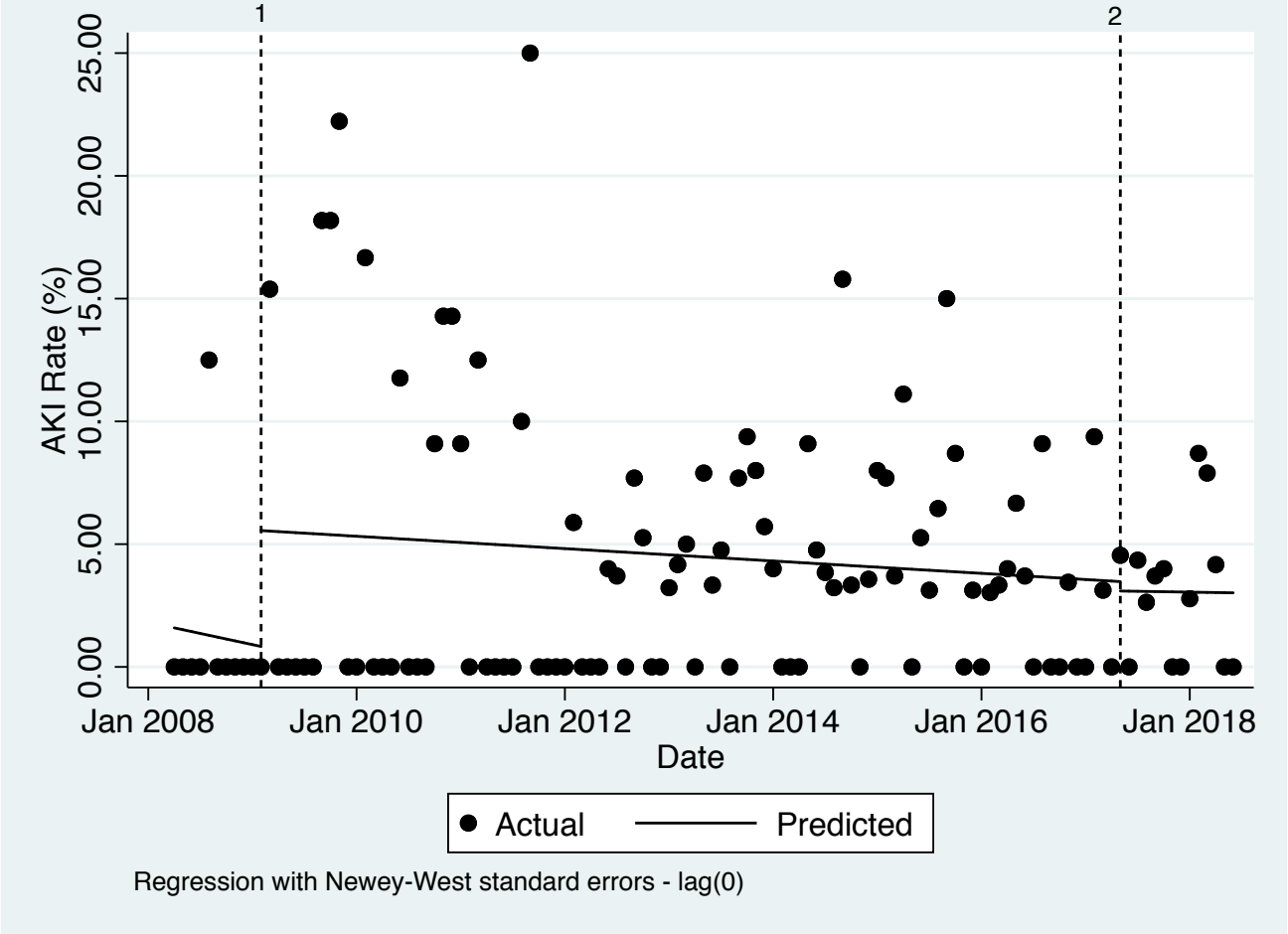


Figure 13: Unadjusted ITS of model 2

Figure 13 and Table 21 show the results of the unadjusted ITS model for seasonality. The results show that there is a significant level change in AKI rate when moving from Copal with 4.5mg/kg of IV gentamicin to Copal with 3mg/kg of IV gentamicin (p=0.011, 95% CI 1.08 to 8.359). There is no change in trend from this intervention and decreasing to no IV gentamicin also shows no level or trend changes with statistical significance.

Table 21: Unadjusted ITS analysis of model 2

AKI Rate (%)	Coef.	Std. Err.	P value	95% Confidence interval	
Pre-trend	-0.076	0.161	0.638	-0.394	0.242
Level change intervention 1	4.719	1.838	0.011*	1.080	8.359
Trend change intervention 1	0.055	0.162	0.736	-0.266	0.376
Level change intervention 2	-0.384	1.407	0.786	-3.171	2.403
Trend change intervention 2	0.015	0.18	0.93	-0.34	0.37

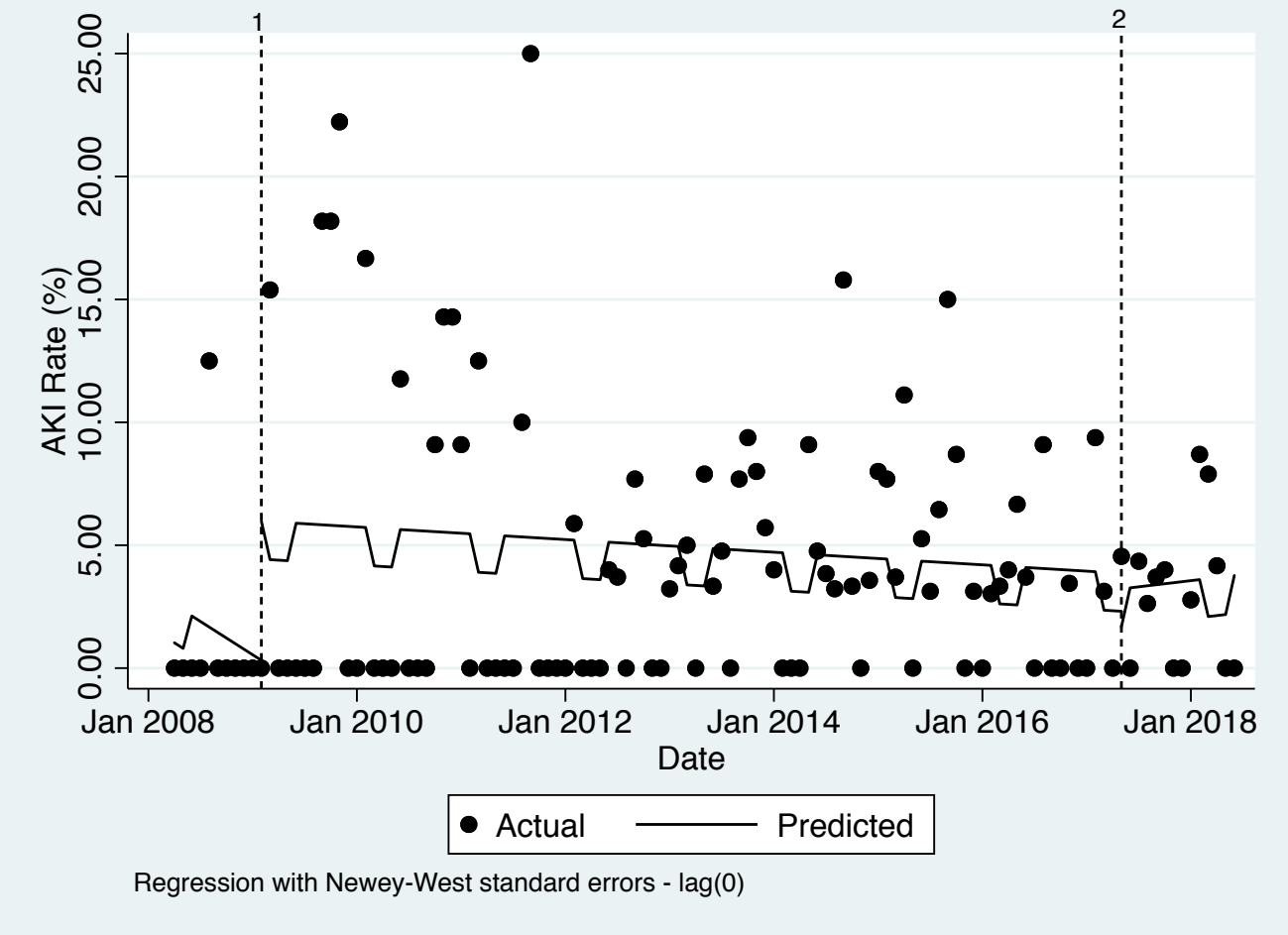


Figure 14: Adjusted ITS for seasonality of model 2

Figure 14 and Table 22 show the results of the adjusted ITS model for seasonality. The results show that there is a significant level change in AKI rate when moving from Copal with 4.5mg/kg of IV gentamicin to Copal with 3mg/kg of IV gentamicin (p=0.004, 95% CI 1.83 to 9.49). There is no change in trend from this intervention and decreasing to no IV gentamicin also shows no level or trend changes with statistical significance.

Table 22: Adjusted ITS analysis for seasonality of model 2

AKI Rate (%)	Coef.	Std. Err.	P value	95% Confidence interval	
Pre-trend	-0.23	0.17	0.199	-0.57	0.12
Level change intervention 1	5.66	1.93	0.004*	1.83	9.49
Trend change intervention 1	0.20	0.17	0.243	-0.14	0.55

Level change intervention 2	-0.64	1.61	0.692	-3.82	2.55
Trend change intervention 2	0.06	0.21	0.766	-0.36	0.48
Season	-1.55	1.03	0.136	-3.58	0.49

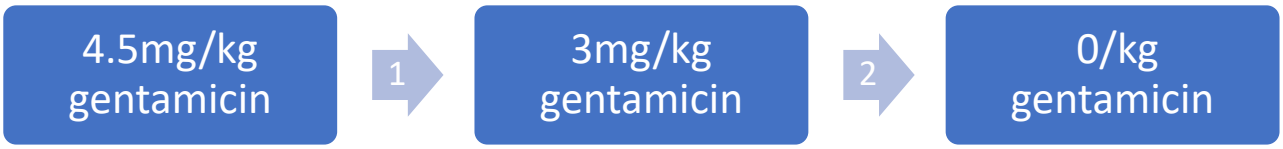
Table 23: Autocorrelation analysis of model 2

Lag	Chi2	P value
1	1.506	0.220
2	2.156	0.142
3	3.797	0.051
4	0.961	0.327
5	0.149	0.699
6	0.010	0.921
7	0.017	0.895
8	0.591	0.442
9	0.138	0.710
10	0.761	0.383
11	0.043	0.836
12	0.307	0.580

There is no statistical evidence of autocorrelation in this analysis up to a lagged value of 12 (table 23).

2.7.3 Model 3 – IV gentamicin doses

This model is for the changing interventions from January 2008 to August 2018 for the below interventions.



A scatterplot of the data over the time is presented to visually inspect the trend and shows decreasing AKI over time (figure 15). The interventions in the above diagram are represented by the lines 1 and 2 respectively

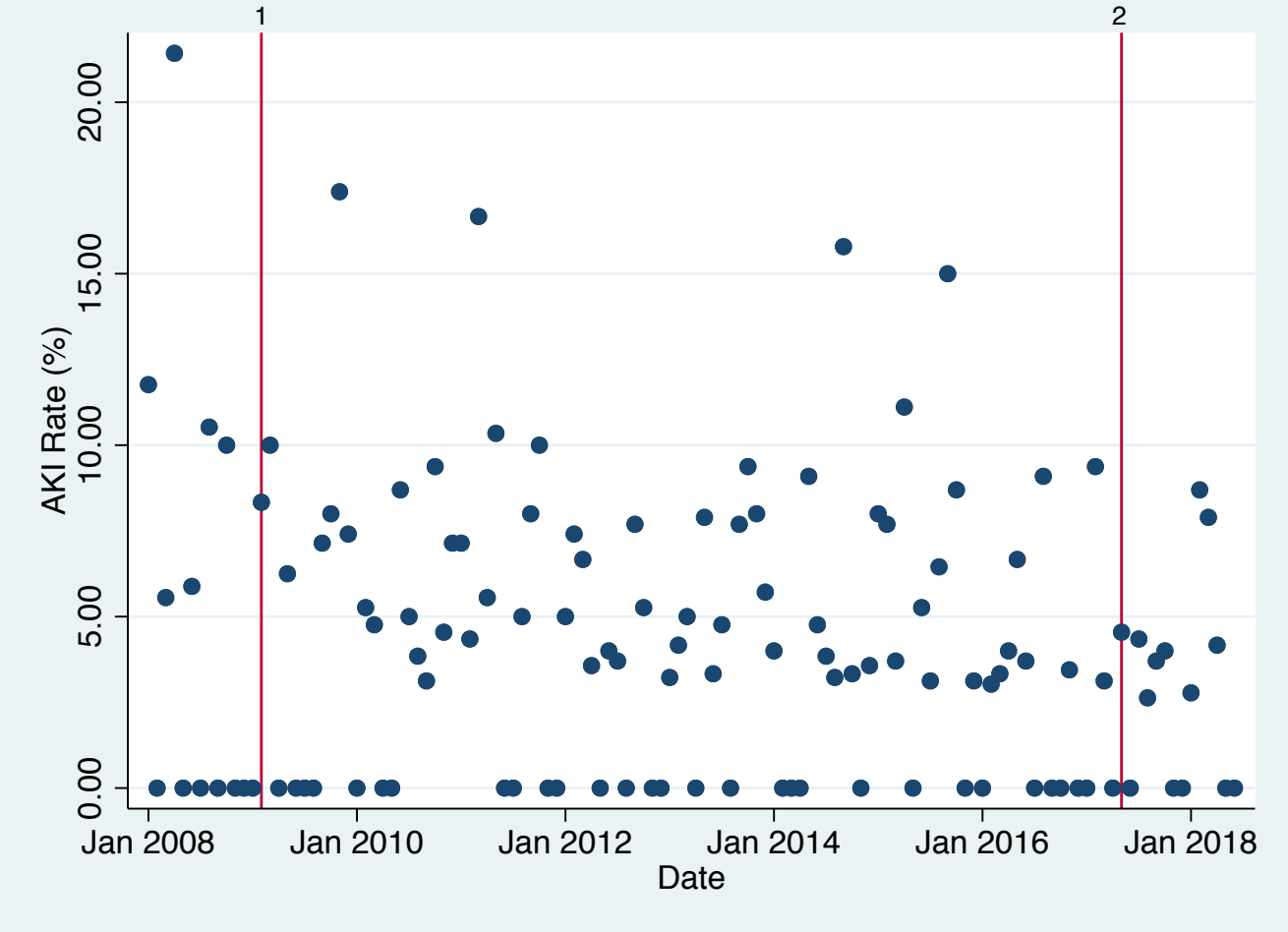


Figure 15: Scatterplot for model 3

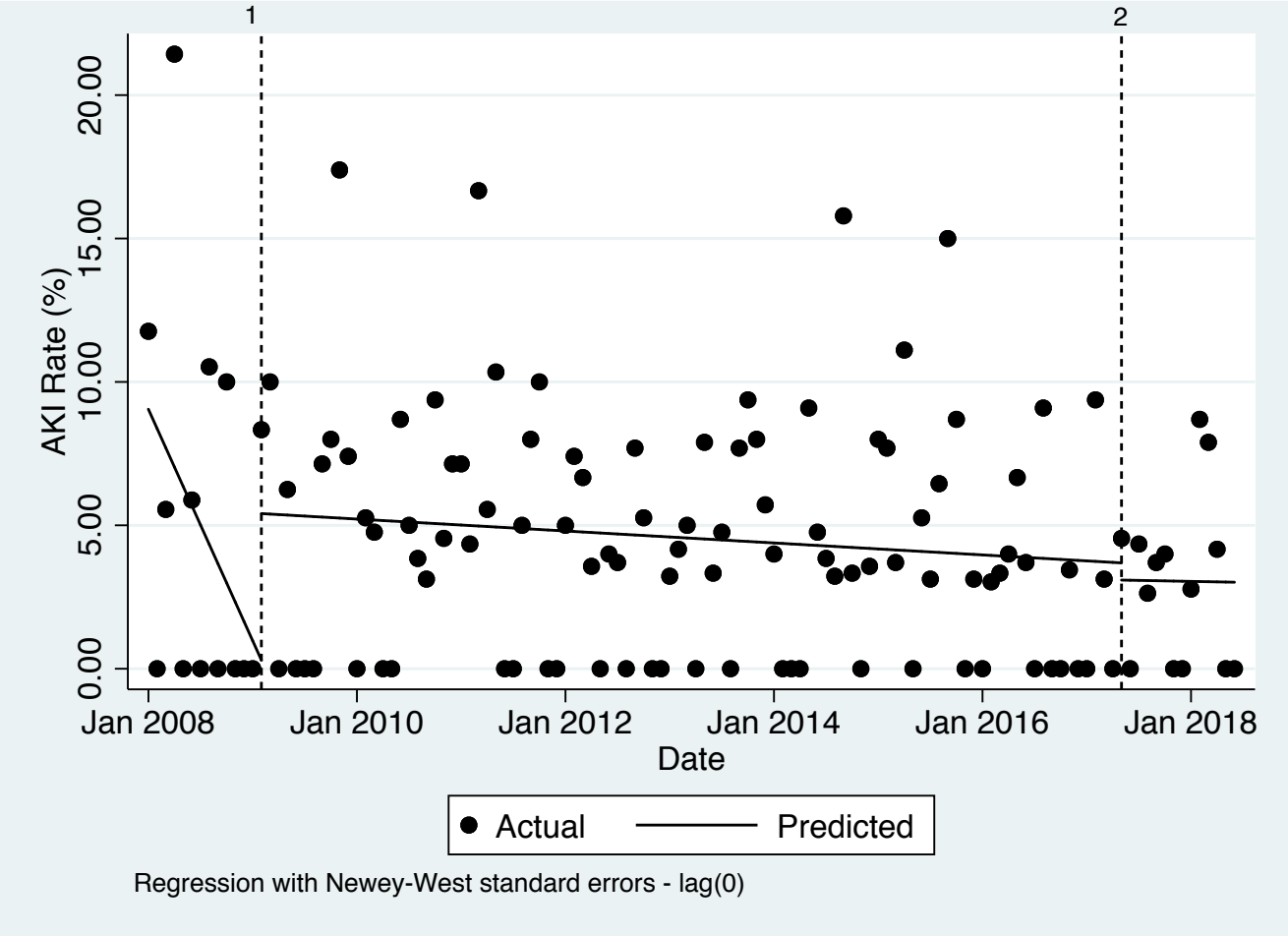


Figure 16: Unadjusted ITS for model 3

Figure 16 and Table 24 show the results of the unadjusted ITS model for seasonality. The results show that there is a significant level change in AKI rate when moving from 4.5mg/kg of IV gentamicin to 3mg/kg of IV gentamicin (p=0.037, 95% CI 0.321 to 9.895). There is no change in trend from this intervention and decreasing to no IV gentamicin also shows no level or trend changes with statistical significance.

Table 24: Unadjusted ITS analysis for model 3

AKI Rate (%)	Coef.	Std. Err.	P value	95% Confidence interval	
Pre-trend	-0.673	0.392	0.089	-1.449	0.103
Level change intervention 1	5.108	2.418	0.037*	0.321	9.895
Trend change intervention 1	0.655	0.392	0.097	-0.121	1.432
Level change intervention 2	-0.600	1.329	0.653	-3.231	2.032
Trend change intervention 2	0.012	0.181	0.949	-0.346	0.369

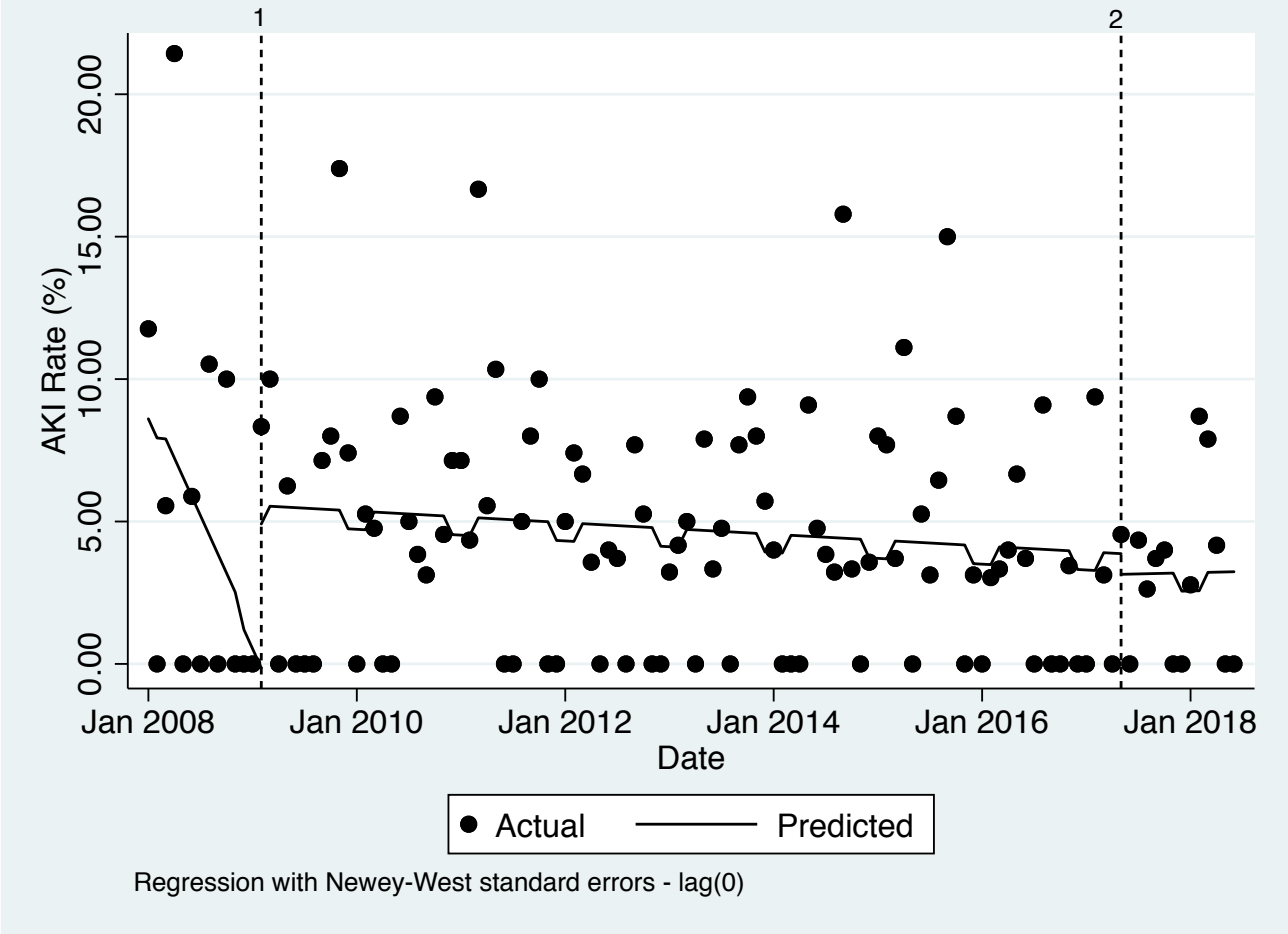


Figure 17: Adjusted ITS for seasonality of model 3

Figure 17 and Table 25 show the results of the adjusted ITS model for seasonality. The results show that there is a significant level change in AKI rate when moving from 4.5mg/kg of IV gentamicin to 3mg/kg of IV gentamicin (p=0.036, 95% CI 0.32 – 9.79). There is no change in trend from this intervention and decreasing to no IV gentamicin also shows no level or trend changes with statistical significance.

Table 25: Adjusted ITS analysis for model 3

AKI Rate (%)	Coef.	Std. Err.	P value	95% Confidence interval	
Pre-trend	-0.67	0.38	0.084	-1.44	0.09
Level change intervention 1	5.05	2.39	0.036*	0.32	9.79
Trend change intervention 1	0.56	0.39	0.092	-0.11	1.42
Level change intervention 2	-0.72	1.36	0.595	-3.42	1.95

Trend change intervention 2	0.02	0.19	0.899	-0.35	0.40
Season	-0.40	0.77	0.406	-2.16	0.88

Table 26: Autocorrelation analysis of model 3

Lag	Chi2	P value
1	0.091	0.762
2	0.989	0.320
3	3.002	0.083
4	0.023	0.879
5	0.454	0.500
6	0.001	0.977
7	0.832	0.316
8	0.002	0.967
9	0.252	0.615
10	1.774	0.183
11	1.004	0.316
12	0.012	0.912

There is no statistical evidence of autocorrelation in this analysis up to a lagged value of 12 (table 26).

2.8 Discussion

This is a retrospective cohort study on the acute kidney injury rate of hip fracture patients that have received surgical treatment; a cemented hemiarthroplasty between January 2008 and June 2018. The study was conceived to support the WHiTE 8 trial's secondary safety analysis.

The primary aims of this study were:

1. To quantify and draw inferences on the rate of AKI as classified by the RIFLE criteria within five days post-surgery in the low dose single and high dose dual ALBC groups

2. To quantify and draw inferences on the rate of AKI as classified by the RIFLE criteria within five days post-surgery with different intravenous gentamicin regimens.

The results section presents two statistical techniques, before and after analysis, and ITS analysis to answer the primary aims. There is no evidence that high dose dual ALBC or different IV doses of gentamicin have a clinically measurable effect on AKI as classified by the RIFLE criteria. The WHiTE 8 trial also showed no differences in site reported complications of AKI between groups and further supports my findings. Table S11 in the supplementary appendix of the WHiTE 8 trial (appendix 7.1.4) shows an AKI rate of 5.1% and 4.5% in single ALBC and high dose dual ALBC respectively.

2.8.1 Before and after analyses

Using before and after statistical techniques the results have shown that I can accept the null hypothesis related to the primary aims of the study. There is no statistically significant difference in AKI rate as determined by the rifle criteria in the first five days post-operatively when comparing Palacos R+G and Copal G+C groups over the study length (table 6). The rate of abnormal rifle classification between patients receiving Palacos R+G and Copal G+C was 5.2% and 4.2% respectively ($p = 0.24$). I originally planned to repeat this statistical test adjusting for comorbidities however thought this unnecessary when inspecting table 6 as there was no trend towards increased AKI in the Copal group despite increased prevalence of comorbidities. In addition to this finding, the results also showed that the different doses of intravenous gentamicin analysed with or without the effect of antibiotic loaded cement shows no statistical difference between groups at five days post-operatively (table 8).

The secondary aims of the study were in assessing rate of admission to critical care in the first 30 days and mortality in the first 30 days. The rate of critical admission in the Palacos R+G and Copal G+C

groups were 3.3% and 2.8% respectively. There was no statistical difference between the two ALBC groups in their admissions to critical care in the first 30 days post operatively (p=0.307) (table 11). The between group analysis (table 12) was statistically significant (p=0.004) but is imprecise due to the wide range in sample size between groups (Range 41-1938). Each subgroup is not representative of the total subgroup population and so a statistically significant figure cannot be accurately interpreted and likely only due to chance especially given the number of statistical tests conducted.

In table 27, the group with the lowest overall dose of gentamicin (group 5) had a critical care admission rate of 5.5% at 30 days whilst the group receiving the highest overall dose (group 1) had a critical rate admission rate of 0% at 30 days. Group 2, 3, and 4 had rates of 1.6%, 2.3% and 3.9% respectively. This dose relationship is in the opposite direction to what was hypothesised and therefore does not support the hypothesis that increasing total dose of gentamicin increases the rate of admission to the critical care unit.

Table 27: Critical care admission in different subgroups

Group	*ALBC and Intravenous Gent*	*Critical care admission rate (%)*
1	Copal with IV gentamicin 4.5mg/kg	0
2	Palacos with IV gentamicin 4.5mg/kg	1.6
3	Copal with IV gentamicin 3mg/kg	2.3
4	Palacos with IV gentamicin 3mg/kg	3.9
5	Copal with no IV gentamicin	5.5

Mortality at 30-days (table 13) showed a statistical difference between Palacos R+G and Copal G+C (p=0.044) and was 8.6% and 6.5% respectively. There was no statistical difference in the subgroup analysis (P=0.264) (table 14). When we look at the mortality of subgroups of ALBC with intravenous gentamicin being a constant factor we see that those patients receiving Copal G+C had lower mortalities compared to patients receiving Palacos R+G (table 28). This is an interesting finding as the population in the Copal G+C had more comorbidities and so a potentially higher chance of mortality. The increased doses of antibiotic in the ALBC may have had a protective effect with regards to surgical site infection which is known to result in up to 50% mortality (Guren et al. 2017; Edwards et al. 2008; Noailles et al. 2016). SSI rates were not monitored in this study and so could have contributed as a confounder to this analysis on mortality.

Table 28: Summary of mortality in subgroups

Intravenous gentamicin dose	*Palacos R+G mortality (%)*	*Copal G+C mortality rate (%)*
4.5mg/kg	10.1	7.3
3mg/kg	8.1	6.6
0mg/kg	-	5.8

2.8.2 Population baseline characteristics

The baseline characteristics between ALBC groups showed a significant difference in rates of comorbidities (Ischaemic heart disease, hypertension, COPD and Alzheimer's disease) indicating a potentially frailer group of patients in the Copal G+C group due to increased comorbidities. A meta-analysis of 10 studies investigating 34 potential factors to predict postoperative AKI in patients undergoing hip fracture surgery showed that positive predictors included being male, advanced age, ischaemic heart disease, hypertension, diabetes and chronic kidney disease (Zhou et al. 2021).

There are no known factors for why the population receiving Copal may have had increased comorbidities as the choice of cement was independent to the overall health of the patient at the time of surgery. Studies suggest a falling prevalence of hypertension and static prevalence of cardiac disease over time (Sinnott et al. 2017; Bhatnagar et al. 2016), which is at odds to our data as the majority of patients received Copal after 2012 whilst those receiving Palacos was before this. This could however be explained by improved detection and diagnosis of these condition in primary care during the study period rather than a true increase in prevalence of the conditions although there is no way I can measure this within my dataset.

The predicted finding would have been that a frailer population in conjunction with increased doses of gentamicin exposure would lead to an increased AKI rate. However, the analysis unadjusted for comorbidities still showed no difference in AKI rate (table 6 and table 8). A potential explanation may be that this is an intention to treat analysis with the assumption that all patients received the stated protocol of ALBC. The higher risk patients would have most likely had dose modification or gentamicin substitution with another intravenous antibiotic. This would lead to an underestimation of the AKI rate in the Copal G+C group and therefore potentially a type 2 error. A per protocol analysis would have been useful to further contrast any potential differences but was outside the scope of possibility with the current methodology used in this study.

2.8.3 Interrupted time series

Three models were created to analyse the data, and each was adjusted for seasonality i.e., winter months. All models clearly show that over the 10-year period there was an overall decreasing trend in AKI. The results are however very different to proposed impact models theorised (figures 6,7 and 8). The results of model 1 show that after accounting for intravenous gentamicin dose there was no significant difference in AKI between Palacos R+G and Copal G+C groups (figure 10 and figure 11). Subsequent modelling (model 2) shows that when ALBC is held constant (Copal G+C), in conjunction with changing intravenous gentamicin concentrations, the only significant level change is when there is a step down from intravenous 4.5mg/kg gentamicin to 3 mg/kg gentamicin. However, this change resulted in an unexpected level increase in AKI which may reflect a degree of imprecision due to the fewer available data points prior to the first change in intervention (figure 13 and figure 14).

As model 1 showed no significant difference between Palacos R+G and Copal G+C in the rate of AKI, a further model was created ignoring ALBC and solely looking at the intravenous concentrations (model 3, figure 15 and figure 16). The results of this again showed a similar outcome to model 2 with an unexpected level change when there was a step down from intravenous 4.5mg/kg gentamicin to 3 mg/kg gentamicin. I think that this again reflects imprecision as highlighted above.

Generally, the ITS analyses have been extremely useful in showing us that the general trends over the time show an improvement in AKI rate in the fracture neck of femur population independent to ALBC or intravenous dosing of gentamicin.

2.8.4 Strengths and weakness

One of the strengths of this analysis is that the methodology of data collection led to an overall missing data rate of less than 1.5%. The missing data was also classed as missing completely at random with no relationship with the outcome investigated. Therefore, in the time being observed the risk of selection bias is very low and the data is representative of the population being investigated.

A significant weakness of before-after statistical analyses techniques is that the analyses do not consider the changing trends on outcome prior to the intervention. In my study this specifically refers to the trend in AKI over time prior to the change in prophylactic antibiotic policy. This analysis is therefore supplemented by a quasi-experimental method of analysis, an interrupted time series. The ITS design is a key strength of my study as it let me take account of the changing trend and helped to

determine the true effect of an intervention change i.e., change in IV dose of gentamicin, or change in ALBC.

This is a large dataset of 3178 patients over a 10-year period and therefore has less potential for outliers to cause imprecision. The sample size for comparisons between ALBC and the use of 3mg/kg of IV gentamicin is large to make robust conclusions. However, when we try to find relationships from subgroup analyses (4.5mg/kg of IV gentamicin for both Palacos R+G and Copal G+C) the data is limited to a much smaller sample size. This imprecision results in difficulty in interpreting conclusions when statistically significant differences are shown e.g., table 12. There was also imbalance in the number of patients and thus data points for ITS analysis of those patients receiving 4.5mg/kg of gentamicin. Imbalance in ITS analyses results in low ITS power within this intervention segment regression (interventions 1 of model 2 and model 3)(Zhang, Wagner, and Ross-Degnan 2011). This may have contributed to the imprecision and resultant unexpected level increase in AKI. Therefore, limited recommendations can accurately be made regarding the use of ALBC with 4.5mg/kg of gentamicin.

The data collection methodology also had some limitations, specifically in allowing insight as to the reasons for critical care admission and cause of death. The admission records to critical care and death certificate are not available electronically and thus to collect this data a case review would have been required. We can only therefore make assumptions regarding this trend.

The most significant confounder for critical care admission and mortality after surgery that we cannot account for is the surgical site infection rate (SSI). Although the increasing doses of intravenous gentamicin and ALBC are not associated with increased AKI in my study, the rates of SSI may have been affected. The FHIT trial was conducted at the NHCT between 2008 and 2012 comparing the deep infection rates between two ALBC groups; Palacos R+G and Copal G+C. During this trial period, patients also received intravenous gentamicin (either 4.5mg/kg or 3mg/kg). The results of this trial showed a significant difference in deep infection rates (3.5% to 1.1%, $p = 0.041$) favouring Copal G+C (Sprowson et al. 2016). The results in my study show a higher mortality rate and admission rate to critical care when using Palacos R+G over Copal G+C and this may be explained by the excess risk of SSI by using an ALBC with lower doses of antibiotics. Consequently, an increased level of deep infection may have had contributed to 30-day mortality and 30-day critical care admissions rather than any changes from AKI.

2.8.5 Data set assumptions

To accept the validity of the analyses there are assumptions that need to be discussed further. My study is analysed under an intention to treat method and may underestimate the differences between groups. Frailer patients with new onset pre-surgery AKI or a history of chronic kidney disease are often withheld IV gentamicin to prevent the risk of worsening renal function. This is done at the discretion of the treating surgeon and anaesthetist. My study assumes that these patients received antibiotics as per the NHCT antibiotic prophylaxis guideline at the time, therefore comparisons between groups may not be accurate. We would expect that that the number of these types of patients presenting to the department monthly remained low and constant over the period, potentially minimising this effect however there is no way to monitor this without reviewing each patient case notes which is not within the remit of this study.

Another assumption is that the total systemic dose of gentamicin that a patient is exposed to was in the order illustrated by table 3 based on my clinical and medical experience rather than patient measured levels. The cumulative dose was made up via the administration of the gentamicin through both local delivery (ALBC) and systemic delivery (intravenously). Published evidence does not show consistency with regards to the amount of systemic absorption of ALBC and is also limited to studies using high dose ALBC for the treatment of periprosthetic infection rather than for SSI prophylaxis. Edelstein et al (2018) study showed that the use of a combination of aminoglycosides (gentamicin + tobramycin) totalling 2.9g per 40g mix of cement (Palacos R+G) showed no serum levels reach above the therapeutic threshold for nephrotoxicity of 2mg/l within the first 8 weeks (Edelstein et al. 2018). Thus, using this understanding, the assumption is that the single biggest contributor to systemic gentamicin exposure to the kidneys comes from the intravenous dose with ALBC only having small additive effects. Hence the assumed cumulative doses are ordered as such in table 3.

2.8.6 High dose ALBC

The WHiTE 8 Copal trial defines the use of Copal G+C as a high dose dual antibiotic loaded cement, however, there is no actual definition as what is classified as high or low dose. Generally, the use of high dose refers to therapeutic levels of antibiotics within each 40g mix of cement. The amount described in published literature greatly varies but is often greater than 2g per 40g mix of cement. A systematic review including 10 observational studies of hip and knee periprosthetic joint infections reported an AKI rate of 4.8% with the majority of the studies using doses greater than 3g of antibiotics within the cement in the treatment of these patients (Luu et al. 2013). Hence the use of Copal G+C which contains 2g/40g mix of cement may not actually be classed as high dose ALBC and thus explain

why the results of this study show no difference in AKI rates. This is of course reassuring and supports my study findings that Copal G+C can be safely used without impacting AKI rate for patients with neck of femur fractures.

2.8.7 Post-operative monitoring for AKI

In this study the time frame attributed to AKI because of antibiotics administration at the time of surgery was five days. The rationale for five days was numerous. Studies of elution of ALBC have shown peak concentrations are achieved a few hours after implantation and plateau after the first 2-4 days (Bistolfi et al. 2011; Edelstein et al. 2018; Kühn 2013). Evidence of intravenous single dose of gentamicin used in primary hip and knee arthroplasty and in neck of femur fractures have shown transient mild AKI's that mostly normalise by day five post operatively (Ahmed et al. 2016; Craig et al. 2012; Bailey et al. 2014). Hence, a period of five days post operatively was decided to be a sufficient time to detect any changes in serum creatinine. Additionally, post operatively bloods are not reliably taken on specific days after surgery. Usually, postoperative day one bloods are taken and depending on the results the next set of routine bloods may be taken between day two and day five. Thus, the benefit of using the first five days is that the risk of missing a trending serum increase in creatinine is minimised.

2.9 Conclusion

The use of prophylactic antibiotics is important in the reducing the risk of SSI. My study has shown that higher doses of gentamicin administered to patients prophylactically via ALBC or intravenously in the doses studies do not result in an AKI. The data set robustly supports that the subgroup of high dose dual ALBC with 3mg/kg IV gentamicin is safe to use with no excess adverse effects on AKI. Additionally, I have also shown that using higher doses of ALBC and IV gentamicin shows no adverse effect on mortality or admission to critical care. Patients with hip fractures requiring a cemented hemiarthroplasty can safely be given gentamicin prophylaxis as routing both systemically and locally within ALBC.

3 Chapter 3: Strategies to improve recruitment rate to the WHiTE 8 randomised control trial

The chapter describes a survey of UK orthopaedic trainees and an original embedded study within a trial (SWAT) that I designed, conducted, and reported. The protocol and results of the study (Nickil Agni et al. 2019; NR Agni et al. 2022) have been published and some of the material is reproduced here. The published papers and supplementary information are available in appendix 7.2.

3.1 Summary

Background

Randomised controlled trials (RCTs) often struggle with various aspects of participant recruitment, including engaging clinicians to recruit effectively, and subsequently fail to reach their target sample size. Studies evaluating interventions to improve recruitment aimed specifically at recruiters to the trial are limited in number.

The RCTs embedded into the World Hip Trauma Evaluation (WHiTE) cohort study use Trainee Principal Investigators (TPis) to help manage and drive recruitment at trial sites. No formalised training or support is provided by central trials units to the TPi. Additionally, following recruitment and consent of an individual to WHiTE trials, trial recruiters received a generic automated email confirming randomisation to the trial with no other communication to influence or incentivise their behaviour to further recruit.

The primary aim of this factorial trial was to evaluate the effectiveness of an educational intervention to TPis and a positive reinforcement intervention via an email (digital) nudge on increasing recruitment. Secondary aims included feasibility of implementing the interventions and surveying TPis on the educational package quality of content, delivery, and ongoing support.

Design

This was a multicentre, open, cluster, 2x2 factorial RCT embedded in the WHiTE 8 RCT, in which research sites were randomised 1:1:1:1 to receive the enhanced TPi package, the digital nudge intervention, both, or neither.

Results

1215 patients were recruited to the WHiTE 8 trial across 20 sites during the SWAT between August 2018 and March 2019. There was a statistically significant interaction between the interventions (IRR 2.09, 95% CI 1.64 to 2.68, $p < 0.001$). There was a statistically significant benefit on recruitment (IRR 1.23 95% 1.09 to 1.40, p=0.001) from utilizing an enhanced TPi education intervention. The digital nudge intervention had no significant impact on recruitment (IRR 0.89 95% CI 0.79 to 1.01, p=0.07).

Within enhanced TPi package sites, the digital nudge had a beneficial effect, while in the standard practice TPi sites it had a detrimental effect.

Feasibility analysis showed the median time to site digital nudge and enhanced TPi set up were one day and 17 days respectively. 353 digital nudges were created taking an average of 12 minutes to construct, log the activity and then disseminate to recruiters. Median induction time for enhanced TPi was 32 minutes and 100% of the group were extremely satisfied with the induction content, delivery, and ongoing support.

Discussion

An education and support programme targeted at surgical TPis involving a digital education package, 1:1 telephone induction and subsequent support package was effective in increasing recruitment in the first six months of trial commencement. There was no evidence for the effectiveness of the digital nudge intervention in isolation, though our results show that when combined with an education programme it leads to enhanced effectiveness of that programme.

3.2 Introduction

RCTs often struggle with various aspects of participant recruitment, including engaging clinicians to get involved effectively, and subsequently fail to reach their target sample size. Many trials are forced to extend trial timelines or, due to insufficient funding, either revise their sample size downwards or close trials prematurely (McDonald et al. 2006; Bower, Wilson, and Mathers 2007; Sully, Julious, and Nicholl 2013; Walters et al. 2017; Charlson and Horwitz 1984). Improving recruitment to RCTs is therefore a significant area for efficiency gains. Randomised and quasi-randomised trials that have targeted methods of improving recruitment to RCTs have been evaluated in a Cochrane systematic review (Treweek et al. 2018). There were limited studies of interventions directed towards healthcare professionals and other persons involved in recruiting participants to clinical trials, thus highlighting a need to evaluate strategies directed towards this cohort.

Clinical trials often recruit participants from multiple research sites. The trial is overseen by a Chief Investigator (CI), (or occasionally Co-CIs) and each site has a delegated Principal Investigator (PI), whose role is to take responsibility for the research activities relating to the trial at that site. Trainee (or Associate) Principal Investigators (TPis) at a research site can work alongside and gain experience from the site PI. Typical responsibilities of a TPi include co-ordination of, and engagement in, the recruitment of patients to the trial at that site. The NIHR have seen the benefit of this role and have recently launched the NIHR associate PI (APi) programme to formalise this role (NIHR 2024). At the time of inception of this thesis (January 2018) the APi scheme did not exist and there were no RCTs assessing the effect of a TPi on recruitment rate to a trial. In addition, the evaluation of this TPi role from a trainee perspective had not been undertaken.

The World Hip Trauma Evaluation (WHiTE) is an initiative to rapidly and efficiently investigate interventions to improve the outcomes of patients requiring hip fracture surgery (Matthew L. Costa et al. 2016). All hip fracture patients being treated in participating centres are approached for consent to be enrolled in the WHiTE cohort, which collects standardised outcome data from participants. This cohort is a valuable tool in which to embed RCTs to evaluate novel treatment options for hip fracture patients. TPis, recruited and managed by the local PI, are being utilised in some of the RCTs embedded in the WHiTE cohort (Matthew L. Costa et al. 2016). A TPi manual (appendix 7.2.9.2) is provided by the management team based at Oxford Clinical Trials Research Unit (OCTRU) with no further education or support. There was therefore the potential to create an enhanced support package for TPis consisting of formal initial education and ongoing assistance to enhance their knowledge and confidence in undertaking the role.

Nudging has been described in chapter 1.4.5 and is a way of influencing an individual's behaviour through an intervention without limiting their choice. In the WHiTE trials, an automated non-specific (generic, non-personalised) email is sent to the research staff at the recruiting centre after each patient randomisation. An additional email sent to the randomising clinician in a timely manner and incorporating features such as personalisation, appreciation for recruitment, and praise may positively reinforce the behaviour of recruiting to a trial. Personalised emails to the recruiting clinician have not been evaluated using an RCT; however, there is evidence that personalised study invites improve patient recruitment in breast cancer survivors (Short, Rebar, and Vandelanotte 2015) and also in invitations for survey research (Heerwegh 2005; Muñoz-Leiva et al. 2010).

In my SWAT I describe a 2x2 factorial, randomised trial evaluating both enhanced training and support for the TPi and personalised, digital nudging to recruiting clinicians to improve recruitment rates. When considering the best way to design my SWAT I decided that conducting an embedded randomised control trial would be the most appropriate choice to measure the effectiveness of my interventions. The drawback being thought that there is a much greater cost to this design type in terms of time and money (Hariton and Locascio 2018). When testing two independent interventions on an outcome e.g., recruitment rate, two separate trials could be delivered, or a three parallel arm trial could be created. However, in the latter, due to a fixed sample size the analysis would result in smaller groups for comparison. One method of testing two interventions in one trial without compromising sample size would be to consider using a factorial trial design (Montgomery, Peters, and Little 2003). This has the advantage of improved efficiency by allowing inclusion of all participants in each intervention analysis and considers the effectiveness of both interventions being run simultaneously. This study method also saves significant time over running two separate studies with the use of a single protocol, ethics permission and participating site governance and setup.

At the time of inception of this SWAT there were no previous research directed towards trainee experience in recruiting to RCTs. When considering the design of any intervention directed towards the TPi, I first had to determine experiences and challenges currently faced by orthopaedic trainees who had been involved with orthopaedic trials in the TPi role. This would help to inform features and content of the enhanced TPi intervention for my embedded study in the WHiTE 8 trial. One challenge for identifying TPis was that there was no easy way of determining which trainees had been involved and which trials utilised the role other than approaching individual trial teams for active and recently completed orthopaedic RCTs. Subsequently, trainees would have to be individually approached which would have been a time-consuming process. This would have resulted in significant delays in finalising a SWAT intervention to implement for the start of WHiTE 8 recruitment.

Given the time constraints and the lack of a national register of orthopaedic TPis at that time, the optimal method of collecting information to help design an intervention directed to trainees to improve recruitment to a RCT was via a national survey of orthopaedic trainees. This is presented as study 1 below and informs the intervention design for my SWAT which is presented as study 2 further in this chapter.

3.3 Study 1: Survey of UK orthopaedic trainees on TPi experience

3.3.1 Aim

The aim was to evaluate the experience and challenges associated with conducting the TPi role to guide the creation of an enhanced Trainee Principal Investigator intervention. A SWAT was planned to be embedded into the White COPAL multicentre RCT to evaluate the effects of the intervention on recruitment rate. All study documents have been approved by the University of York, Health Sciences Research Governance Committee. Approval ID: **HSRGC/2018/266/C** (appendix 7.2.4)

3.3.2 Methodology

3.3.2.1 Design

Nationally, orthopaedic trainees are organised into post graduate deaneries who are responsible for medical education and training. Each deanery has a speciality programme coordinator representing orthopaedics who was contacted to disseminate the survey to all orthopaedic trainees in their region.

The main areas the survey covered included:

- General question regarding experience as a trainee principal investigator in orthopaedic trials
- Methods of recruitment and training undergone to carry out the role
- The trainees personal experience regarding if they felt valued as a recruiter
- Challenges and logistical problems related to undertaking a TPi role.
- Willingness to participate again as a TPi

The full survey is available in appendix 7.2.7.

3.3.2.2 Participants

The participants were UK orthopaedic trainees who may have had previous experience as a TPi in delivering an orthopaedic RCT however this was not a pre-requisite. Speciality programme coordinator representing orthopaedics for each training region were contacted to disseminate the survey link. Additionally, the British Orthopaedic Trainees Association (BOTA) included the link in their monthly newsletter which was sent to all registered members. There was no power attributed to the survey as a sample size calculation was not undertaken. The survey was sent to all orthopaedic trainees for consideration to participate.

No expenses or monetary incentive were given for participation in this survey. A certificate of completion was offered to show engagement with research for portfolio and revalidation purposes for the trainee. This was offered as an option at the end of the survey and was entirely optional.

3.3.2.3 Inclusions and exclusions

All Orthopaedic trainees were included. These will mostly be trainees at a Specialist Registrar level but may include those out of programme, core trainees and those in locum appointment for service (LAT) posts.
All other specialities were excluded.

3.3.2.4 Survey

The survey was distributed through email by the speciality programme coordinator or via BOTA newsletter to all registered members. The orthopaedic trainee was able to access the survey by clicking on a weblink in the email which took them directly to the survey. No trainee was emailed directly by myself, and an information sheet was provided in the email with my contact number and email address if required by the participant. The information also detailed how the data was used, distributed, and confirmed that the individual will not be identified, and anonymity will be protected (appendix 7.2.6). The first page of the survey was a summary information sheet with a consent check box at the bottom. This box needed to be ticked and agreed with before able to start answering the survey questions.

The survey was created using the website 'Qualtrics' (Qualtrics 2018); which also enabled paper versions of the survey to be printed if participants wished to submit via a postal address given in the email. Burden was kept to a minimum as the survey was delivered and completed electronically. The time for completion was unlikely to be problematic as the survey took no more than 2-10 minutes to fill out. The survey was disseminated on the 4$^{th\ of}$ June 2018 and reminder emails were sent at 2 weeks but nothing further following this.

3.3.3 Results

The survey link was accessed by 32 people of which 31 consented to participate in the study. 28 participants were registrars with training numbers and 3 were core trainees.

21 participants (67.6%) reported that they were aware of the TPi role and how it was used, and 10 participants (50%) were either actively participating or had completed a role as a TPi. Within the group of 10 who were not aware of the role seven (70%) and nine (90%) wanted more information about it and considered getting involved in the future respectively.

Within the subgroup of 10 who were in an active or completed role as a TPi, nine (90%) were offered the role by the trial team or their clinical supervisor whilst one person sought out the opportunity. 44% did not receive any formal training and of the 56% that did, the training offered was simply the study protocol and GCP training. Trainees found that reading materials and presentations were useful and

suggested improvements included more specific information about the TPi role, introductory meetings, and monthly meetings. Five participants (50%) felt they made a difference to trial recruitment and 100% of those with experience in the role said that they would do it again.

The main challenges that participants felt in recruiting to trials from freetext entry included not being available to recruit, surgeon equipoise and challenges in understanding the different consent pathways in recruiting patients to a trial.

3.3.4 Discussion

Although participation in this survey was low, it did highlight some interesting challenges and improvements I could utilise in designing my complex educational intervention directed to TPis.
Participants felt that written information and formal presentations were useful and so this element was included in the enhanced TPi package. Additional written content with regards to how to manage and function in the role along with regular meetings at the start of the role with and subsequent monthly meetings were also features that I decided to include.
Recruiting to trauma trials is often challenging as there are different consenting processes for those with and without capacity. There are also different consenting processes for patients that are recruited under the local site principal investigator for patients without capacity. This can all lead to some confusion in the recruiting process (as highlighted in the survey) and so literature and training to support this challenge was considered when designing the complex education intervention

3.3.5 Summary

The survey showed that the role of the TPi was already in use in orthopaedic RCTs and feedback given regarding the role was positive. There was also the desire for those who were and were not involved to have further opportunities in participating in the role in future trials. This survey helped to inform training material and in designing the intervention directed towards TPis for the EnTraP factorial randomised control trial.

3.4 Study 2 - EnTraP: A factorial randomised control trial

3.4.1 Aim

This SWAT investigated two different methods of enhancing recruitment: introducing a TPi with an enhanced training and support package to a site, and personalised, digital nudge to healthcare professionals involved in patient recruitment. The SWAT was implemented in a large, UK, multicentre orthopaedic RCT, the WHiTE 8 trial (ISRCTN15606075).

The primary aim was to:

- Assess the effectiveness of an enhanced TPi package, and of a digital nudge, on the total number of patients recruited to the WHITE 8 trial in the first six months of recruitment at a site.

The secondary aims were to:

- Determine the time taken to implement each intervention from the time recruitment commences at the site.
- Compare the randomisation rate of eligible participants in each of the intervention groups.
- Gain feedback on the trainee perspective of the TPi role via a survey.
- Determine the time needed to conduct the 1:1 educational training session for TPis.
- Determine the required time and method of additional contact for peer support of the TPis.

3.4.2 Methods

3.4.2.1 Trial design

This was a multicentre, cluster, 2x2 factorial RCT embedded in the WHiTE 8 COPAL RCT, in which research sites were randomised 1:1:1:1 to receive the enhanced TPi package, the digital nudge intervention, both, or neither (table 29). This was an open trial and participating sites; the data analyst and trial team were not blind to allocation. The first site was randomised into the SWAT on 22/08/2018 and follow-up was completed on 20/09/2019. The trial was approved by the NHS Wales Research Ethics Committee and York University Research Governance committee (appendix 7.2.4) and reported in accordance with the trial protocol and Consolidated Standards of Reporting Trials (CONSORT) statement.

To satisfy the pre-requisites for a factorial trial design, I had to consider the likelihood of an interaction between the enhanced TPi, and digital nudge interventions being assessed. Based on experience of orthopaedic multicentre RCT's at both the York Trials unit and OCTRU most patients recruited to trials

were by departmental research nurses trained in managing and conducting the specific study. The TPi role at the time of inception of this SWAT was gaining increasing traction with trainees contributing to recruitment but certainly making a much smaller volume of total recruitment. I felt that as the TPi intervention was directed more towards education of a maximum of 10 individuals whilst the nudge intervention was directed to all randomisers (estimating 300 participants or more), there would be minimal risk of an interaction effect although not impossible. There were no other studies replicating these interventions, therefore no established literature that could guide me with assessing this either. As part of the methodology the plan was to formally assess the interaction ratio between the variables and an analysis with and without interaction terms was considered. This would also then help to guide study design and future work from the output of this study.

The first 20 WHiTE centres recruiting to the WHiTE 8 trial were included as the trial management and follow up had to be completed before the lead author (NA) returned to clinical practice. The recruitment centre where the CI for the factorial SWAT (author NRA) was based was excluded to prevent bias.

Table 29: Factorial Design of the EnTraP trial

	Enhanced TPi	**Usual Practice**	**Digital Nudging Comparison**
Usual Practice	**Group A**	**Group C**	
	Enhanced Trainee PI	Standard Practice	*A+C*
Digital Nudging	**Group B**	**Group D**	
	Enhanced TPi Nudging	Nudging	*B+D*
Enhanced TPi Comparison	*A+B*	*C+D*	

3.4.2.2 SWAT Interventions

Usual practice for TPis: The usual method of identifying patients suitable for recruitment to a WHiTE trial is via daily trauma meetings attended by a multidisciplinary team and may include consultants,

trainees, research nurses, ward nurses, theatre staff and physiotherapists.

TPis were not mandated at individual sites but were recommended by the trial management team at site initiation visits to the participating site. A TPi manual was made available with specific information regarding the role but no further involvement thereafter.

Usual practice following successful randomisation of a participant*:* An automated email was generated to local research teams after each successful patient randomisation via an online randomisation portal. There were monthly email updates to local research teams regarding trial processes and progress. The usual incentive to randomisers is acknowledgement as a collaborator in the WHiTE 8 trial publication and trainee orthopaedic surgeons, in addition, receive evidence of randomisation through certification.

Enhanced TPi*:* To develop an enhanced TPi package, a survey was carried out with orthopaedic trainees nationally. The methodology, results and analysis of this survey is described earlier in the chapter (study 1). The results of the survey helped to inform and modify features of the complex intervention package.

The Enhanced TPi intervention was a complex intervention involving:

1. **Education**: 1:1 telephone training by the WHiTE 8 research fellow to the TPi covering:
    a. Background to the WHiTE 8 trial
    b. TPi role and benefits of participating
    c. How to effectively perform the TPi Role
    d. How to recruit and randomise to the WHiTE 8 trial
2. **Peer support**: Support and advice by the WHiTE 8 research fellow through SMS/WhatsApp messaging with follow up emails and telephone calls if required for problems related to carrying out the role.
3. **Digital supplementary information:** Provision of supplementary material by email including:
    a. Induction agenda
    b. TPi manual and new TPi checklist
    c. Induction summary presentation
    d. WHiTE 8 consent flow diagram and protocol
    e. TPi contact information consent form

The educational session involved an induction into the TPi role run by the WHiTE 8 research fellow (me). This was an estimated 40-minute telephone session covering all aspects of the role outlined in an agenda emailed to trainees with additional supplementary material one week before the induction time slot (appendix 7.2.9 and 7.2.10).

The TPis were messaged via SMS or WhatsApp monthly to ask if there are any problems with recruitment that they needed support with. The method of further contact e.g., SMS/WhatsApp, Email or telephone call was dependent on the issue highlighted and may have involved the local PI or CTU. A record of these communications was kept by the WHiTE 8 research fellow (me).

Digital Nudging: A standardised email nudge was sent each time a health care professional randomised a participant to the trial (appendix 7.2.11).

Each email included nudges with these features:

- Personalisation (clinician is named)
- Encouragement through praise to continue recruiting
- Statement of appreciation for recruiting a patient to the WHiTE 8 COPAL trial
- Digital nudge within 72 hours after recruitment

The aim was to email the recruiter within 72 hours and where a clinician had recruited multiple patients in the period, only one email was sent referring to the number recruited in the period. The same was for recruitment occurring between Friday 5pm to Monday 8am. This reduced the burden of emails sent to research staff.

3.4.2.3 EnTraP intervention summary

The activity for each intervention is summarised below for ease of reference (table 30)

Table 30: Summary of EnTraP trial intervention activity

ACTIVITY	**USUAL PRACTICE**	**ENHANCED TPi**	**DIGITAL NUDGE**
Identify TPi for the trial	Local Principal Investigator	Local Principal Investigator	
Training of TPi regarding how to perform their role	Local Principal Investigator TPi Manual	Local Principal Investigator WHiTE 8 Fellow via 1:1 telephone induction TPi manual	

		Induction summary presentation	
Training TPi regarding the WHiTE 8 trial and consenting procedures	Local Principal Investigator	Local Principal Investigator WHiTE 8 Fellow via 1:1 telephone induction WHiTE 8 consent flow diagram and protocol provided	
Peer Support of TPi		Monthly contact by WHiTE 8 fellow WHiTE 8 Fellow can be contacted by TPi as required by SMS/WhatsApp/Email	
Digital information provided to TPi	TPi Manual	Induction agenda TPi manual and new TPi checklist Induction summary presentation WHiTE 8 consent flow diagram and protocol TPi contact information consent form	
Identifying patients for the trial	Trauma meeting	Trauma meeting	
Confirmation of randomisation	Automated email to recruiting centre		Automated email to recruiting centre Additional personalised email to randomiser to the trial

3.4.2.4 Outcome assessment

The primary outcome measure was the total number of patients randomised, from each site, in their first six months of recruitment to the WHiTE 8 COPAL trial. Six months was considered the optimum time to evaluate this intervention as trainee orthopaedic rotations run in 6-month blocks and thus there was no guarantee that the same TPi would carry on in the role beyond 6 months. Randomisation data were routinely collected by the WHiTE trial management team monthly.

Site setup details including activation date, date of first patient recruited, and dates of implementation of each SWAT intervention were recorded on an Excel spreadsheet by myself. This allowed for calculation of time taken to implement each intervention from centres commencing recruitment. Conversion rate from screened population was collected monthly from the main trial database.

The trainee perspective of their role was collected through a TPi Qualtrics survey at the end of the SWAT trial period sent via email (appendix 7.2.8). Responses were based on a 5-point Likert scale ranging from "not very satisfied" to "extremely satisfied". The research fellow maintained a time log for delivering the TPi education intervention and a log of communication for peer support during the period of the SWAT.

3.4.2.5 Participants

As in many SWATs, a power calculation was not undertaken as the number of participating sites was fixed and driven by the needs of the host trial. The first 20 WHiTE centres recruiting to the WHiTE 8 site were included in the SWAT. Further sites were not included due to time constraints (i.e., SWAT CI (lead author NRA) was returning to clinical practice and would not be able to manage the SWAT on a day-to-da basis).

3.4.2.6 Randomisation

The WHiTE centres were randomised 1:1:1:1 by minimisation to one of the four groups (Table 31) to balance key baseline characteristics of: cluster size (the expected number of hip fractures requiring hemiarthroplasty in a year at the site; <300/≥300, expected monthly recruitment based on past performance in other WHiTE trials as a recruiting centre (<9/≥9 patients per month), and co-recruitment to the WHiTE 5 trial which is within the same patient population (Y/N). The WHiTE 5 trial was used as a minimisation factor as patients could only be recruited to one trial (WHiTE 5 or WHiTE 8) and those sites the conducted both studies would have lower recruitment rates to individual trials and thus was an important factor to balance across intervention arms. Self-reported site feasibility questionnaires completed by the recruitment centres were used to collate these data. Randomisation

was done by specialist computer software MinimPy (Saghaei and Saghaei, 2011) using the "biased coin" method. Randomisation was done by me on the day that a site recruited their first patient to account for the lag from site activation to first recruitment.

3.4.2.7 Statistical analysis

Analysis was conducted in STATA v15 on an intention-to-treat basis. Baseline data relating to the sites (including the minimisation factors) are summarised for the four groups as randomised. No formal statistical comparison of baseline data was undertaken.

The number of participants recruited per site was summarised. A Poisson regression model, containing the two interventions (enhanced TPi and digital nudge) and the three minimisation factors (cluster size and expected number recruited per month were included in their continuous form) was undertaken. Adjusted incidence rate ratios (IRRs) and associated 95% confidence intervals (CIs) and p-values were obtained from this model. I undertook an interaction test between the two interventions to see if each tested intervention influenced each other at the participating sites.

Secondary outcomes including time to commence intervention, time required to run the education intervention and communication time and methods used for the peer support aspect of the intervention, were reported descriptively.

3.4.3 Results

3.4.3.1 Baseline data

The first 20 sites recruiting to the WHiTE 8 trial opened between 16th August 2018 and 21st February 2019 and were randomised into the SWAT between 22nd August 2018 and 20th March 2019, an average of 14.9 days (SD 17.0) after site activation. Six sites were randomised to usual practice, four to digital nudge only, and five each to TPi only and TPi plus digital nudge. The overall expected mean recruitment rate per site was 8.0 patients per month (SD 3.9) (Table 31). Mean cluster size was 278.5 (SD 113.1) and four sites were co-enrolled into the WHiTE 5 trial.

Table 31: Baseline data for sites involved in EnTraP

MINIMISATION FACTOR	TPI + DN (N=5)	TPI ONLY (N=5)	DN ONLY (N=4)	UP (N=6)	TOTAL (N=20)
CLUSTER SIZE					
MEAN (SD)	338.6 (125.0)	281.6 (118.1)	233.5 (113.6)	255.8 (106.5)	278.5 (113.1)
<300, N (%)	3 (60.0)	2 (40.0)	3 (75.0)	4 (66.7)	12 (60.0)
≥300, N (%)	2 (40.0)	3 (60.0)	1 (25.0)	2 (33.3)	8 (40.0)
EXPECTED MONTHLY RECRUITMENT					
MEAN (SD)	9.0 (6.5)	8.6 (1.9)	7.0 (2.9)	7.5 (3.5)	8.0 (3.9)
<9, N (%)	3 (60.0)	2 (40.0)	2 (50.0)	3 (50.0)	10 (50.0)
≥9, N (%)	2 (40.0)	3 (60.0)	2 (50.0)	3 (50.0)	10 (50.0)
CO-RECRUITMENT TO THE WHITE 5 TRIAL, N (%)					
YES	1 (20.0)	1 (20.0)	1 (25.0)	1 (16.7)	4 (20.0)
NO	4 (80.0)	4 (80.0)	3 (75.0)	5 (83.3)	16 (80.0)

TPi = trainee principal investigator; DN = digital nudge; UP = usual practice

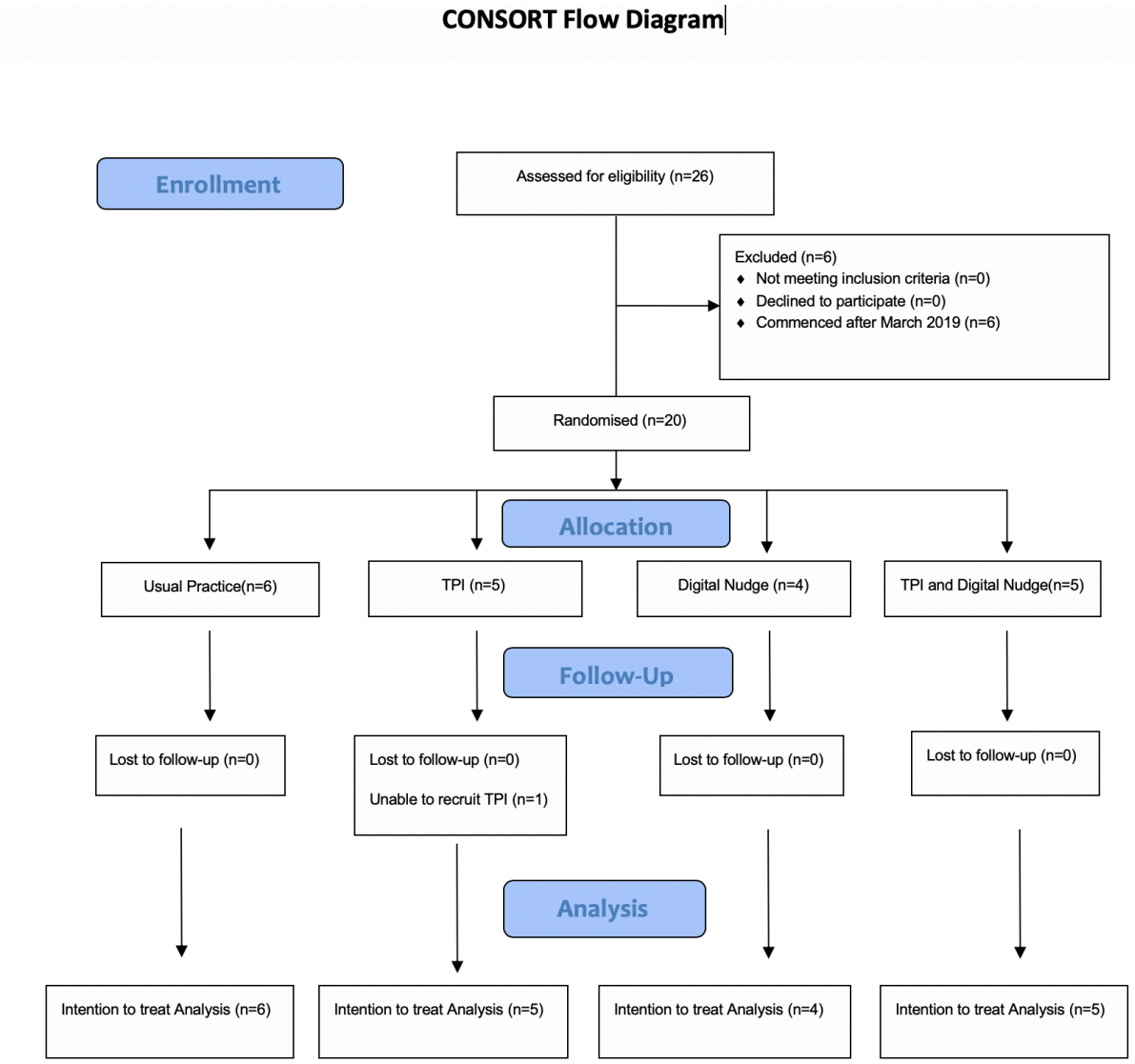


Figure 18: CONSORT flowchart for EnTraP trial

3.4.3.2 Primary outcome

1215 patients were recruited to the WHiTE 8 trial across 20 sites during the SWAT intervention period. The total recruitment figure for each site by group is summarised in Table 32. There were 379, 279, 147 and 410 patients recruited in the 6-month period in the Usual Practice, TPi, Digital Nudge, and, Both TPi and Digital Nudge groups, respectively. The total number of patients recruited over six months in the enhanced TPi package group (10 sites) was 689 (mean 68.9 per site) compared to 526 (mean 52.6 per site) in the 10 centres not allocated to receive this intervention. The total number of patients recruited over six months in the Digital Nudge group (9 sites) was 557 (mean 61.9 per site) compared to 658 (mean 59.8 per site) in the 11 centres not allocated to receive this intervention.

Table 32: Site recruitment as stratified by group randomisation

Usual practice		TPi		Digital nudge		Both interventions	
Site	Recruited	Site	Recruited	Site	Recruited	Site	Recruited
B	91	D	81	F	21	A	117
C	46	H	51	I	65	G	98
E	43	L	48	O	19	J	108
K	69	M	68	P	42	N	41
R	100	S	31			Q	46
T	30						
TOTAL	379		279		147		410
Mean (SD)	63.2 (28.2)		55.8 (19.3)		36.8 (21.5)		82.0 (35.8)

From the primary Poisson regression model (no interaction term) the main effect of the enhanced TPi intervention was a statistically significant benefit on recruitment (IRR 1.15 95% CI 1.02 to 1.29, p=0.02). The digital nudge intervention had no significant impact on recruitment (IRR 0.95 95% CI 0.85 to 1.07, p=0.39).

In the Poisson model including an interaction between the two interventions, the main effect of the enhanced TPi intervention was IRR 1.23 (95% CI 1.09 to 1.40, p=0.001) and of the digital nudge intervention was IRR 0.89 (95% CI 0.79 to 1.01, p=0.07). There was a statistically significant interaction (IRR 2.09 95% CI 1.64 to 2.68, p < 0.001). There is a qualitative interaction in that the addition of the digital nudge is beneficial in the enhanced TPi sites (IRR 1.29, 95% CI 1.11 to 1.51, p=0.001) but detrimental in the standard TPi sites (IRR 0.62, 95% CI 0.51 to 0.75, p<0.001).

Table 33: Incidence Rate Ratio between the intervention and participant recruitment to WHiTE 8 trial

	IRR	95% CI	p Value
Intervention main effects[1]			
Enhanced TPi	1.15	1.02 to 1.29	0.02
Digital nudge	0.95	0.85 to 1.07	0.39
Intervention main effects[2]			
Enhanced TPi	1.23	1.09 to 1.40	0.001
Digital nudge	0.89	0.79 to 1.01	0.07
Simple effect of DN within TPi sites[2]	1.29	1.11 to 1.51	0.001
Simple effect of DN within non-TPi sites[2]	0.62	0.51 to 0.75	<0.001

[1]Obtained from a Poisson model without the interaction; main effects of each intervention adjusted for the other, and the minimisation factors.

[2]Obtained from a Poisson model with the interaction; main effects of each intervention adjusted for the other, and the minimisation factors.

3.4.3.3 Secondary Outcomes:

From the 557 patients recruited at sites allocated to receive the digital nudge intervention, 353 nudges were created for the recruiters. Median time to first nudge from first randomisation at the site was one day (range 0-3). 224 (63.5%) of the nudges were for single randomisations, while 129 (36.5%) were for multiple randomisations conducted over a 72-hour period (relating to 333 randomisations, mean 2.6 per nudge). Seven of the 353 nudges created (2.0%) were unable to be sent due to the lack of an email address despite two follow up emails to local research teams. The average time to construct a nudge, log the activity and then disseminate was 12 minutes. 53 nudges (15.0%) were sent 72 hours after randomisation. Of these late nudges reasons for protocol deviations include: swat CI on annual leave (n=25, 47.2%), CI clinical commitments (n=17, 32.1%), delay from local centres in retrieving email addresses (n=7, 13.2%), and unknown (n=4, 7.5%).

Nine TPis were recruited from the ten sites that were randomised to the enhanced TPi package intervention. Median time for identification and induction of TPis was 17 days from randomisation to a study group (range 9-63). Median induction time for the enhanced TPi was 32 minutes per TPi (range 20-50). A log of monthly enhanced TPi follow up (Table 34), showed that out of 45 points of contact across all sites randomised to the intervention, 31 (68.9%) had “no issues”, six (13.3%) received “no response”, four (8.9%) had “clinical issues that were able to be resolved”, three (6.7%) had local research staff issues that could not be solved centrally and one (2.2%) had research issues that could be resolved centrally.

Table 34: Enhanced TPi log of follow up

TPi	TPi month 1	TPi month 2	TPi month 3	TPi month 4	TPi month 5
1	Clinical Issues - pending resolution	Clinical Issues - resolved	No issues	No issues	No issues
2	No issues	No issues	No issues	No issues	No issues
3	Clinical Issues - resolved	No issues	No issues	Clinical Issues - resolved	No issues
4	No issues	No issues	No issues	No issues	No issues

5	No issues	Research process questions - resolved	No issues	No issues	No response
6	Research Staff sickness - unable to resolve centrally	Research Staff sickness - unable to resolve centrally	Research Staff sickness - unable to resolve centrally	No response	No response
7	No issues	No issues	No issues	No issues	No issues
8	No issues	No issues	No response	No response	No response
9	No issues	No issues	No issues	No issues	No issues

Among the 20 centres running the WHiTE 8 trial during the intervention period there were 17 TPis identified from delegation logs. The response rate for the follow up survey was 52.9%. Nine TPis completed follow up surveys of which seven had received the enhanced TPi intervention (77.7%). All TPis were very satisfied or extremely satisfied with their inductions in explaining the purpose, consent, role of TPi and benefits of becoming a TPi. Amongst the enhanced TPi group 100% of the responders were extremely satisfied with the induction process and felt "extremely supported" with regards to monthly follow-up. Suggested improvements were generic UK TPi education workshops and e-learning modules to help reinforce and discuss key issues that arise across UK Orthopaedic trials.

The proportion of patients recruited as a percentage of the screened population was not analysed due to inadequate data retrieval from base site screening logs.

3.4.4 Discussion

This 2x2 factorial SWAT is the first randomised trial to investigate the effects of an enhanced TPi support package with or without the addition of a personalised digital nudge on recruitment rates; it was embedded within a large orthopedic RCT. The combined use of enhanced TPi and Digital Nudging showed significant interaction (IRR 2.09 95% CI 1.64 to 2.68, $p < 0.001$) in this trial.

In both Poisson models (without and with intervention interaction), sites that received an enhanced TPi training and support package had a significantly increased rate of patient recruitment to the WHiTE 8 trial over six months *(*IRR 1.15, 95% 1.02 to 1.29, p=0.02 and IRR 1.23 (95% CI 1.09 to 1.40, p=0.001 respectively). There was excellent engagement with all aspects of the intervention by TPis: 90.0% participated in the induction activity and 86.7% in the monthly follow up communication indicating that participants were engaged in WHiTE 8 trial recruitment for the entire six-month duration of the

SWAT. The use of increased trial centre coordination through on-site visits has been shown not to impact patient recruitment (Liénard et al. 2006), however, I have shown that an educational package can be delivered more conveniently to a trainee via off-site methods.

The follow up questionnaire also highlighted no suggested areas for improvements in how the intervention was conducted. The monthly follow-up revealed 5 time points at which CI involvement was needed to address clinical and research issues. Although this represents only 11.1% of the follow up points, all trainees felt "extremely supported" and this may have contributed to the increased recruitment at these sites.

There was no significant difference in six-month total recruitment at sites allocated to the digital nudge intervention in both Poisson models without or with the intervention interaction (IRR 0.95, 95% 0.85 to 1.07, p=0.39 and IRR 0.89 (95% CI 0.79 to 1.01, p=0.07 respectively). In terms of feasibility, the intervention had a median lag set up time of one day from first patient recruitment and delivery of the nudge averaged 12 minutes from construction to dissemination including logging the activity. One other study investigated an additional communication strategy directly to clinical sites compared to usual practice of little communication from central trial co-ordinators and found no difference in the recruitment rates; consistent with my results. (Monaghan et al. 2007)

There was a qualitative interaction between the two interventions where the addition of the digital nudge was beneficial in the enhanced TPi sites (IRR 1.29, 95% CI 1.11 to 1.51, p=0.001) but detrimental in the non TPi sites (IRR 0.62, 95% CI 0.51 to 0.75, p<0.001). This may be due to the combined promotion of the host trial at centres by having two interventions directed towards the same recruiting population. It is not clear why the detrimental effect in the non TPi sites occurred as it is not clear from any of the other gathered information in the study.

3.4.5 Strengths and weaknesses

The study design was a strength with additional positive features including a protocol in advance that was registered in the SWAT repository with a statistical analysis plan. The contact information available from delegation logs and local research nurse input was robust enough to ensure that 98% of nudges were disseminated to the respective WHiTE 8 trial recruiter who randomised a participant to an intervention arm. The protocol deviations for nudging beyond 72 hours were relatively high at 15% but 79% (42/53 cases) were due to unavailability of the WHiTE 8 research fellow (me) who acted as the SWAT CI delivering the intervention. Therefore, these deviations are potentially avoidable in future trials if the SWAT is conducted by the CTU team managing the host trial with multiple personnel.

The number of sites available to be randomised to interventions in this factorial trial was fixed and thus a low sample size was a limitation. However, 95% of sites randomised were able to run the interventions investigated thus minimising any imprecision in the intention-to-treat analysis. The minimisation factors of cluster size and predicted recruitment could arguably closely correlate thus being considered a single minimisation variable i.e., those centres with higher incidences of hip fractures per year may be better recruiters to this clinical trial due to increased opportunity for recruitment. However, from our experience from previous trials within the WHiTE cohort framework there is no obvious relationship between the size of the recruitment population and performance of the recruiting site and thus having this variable as independent variables ensured balanced randomisation groups.

A weakness of this trial is that there was only one person involved in training and supporting the TPis and they were also a surgical trainee; thus, there is a generalisation issue that others may not be sufficiently motivated or skilled to deliver the training and support or that TPis may not respond as well to the interventions not being delivered by a peer. Consequently, this intervention ought to be replicated in further trials using different personnel to deliver the training and support.

3.4.6 Future work

These results are widely generalisable to UK multicentre surgical trials as the methodology of centralised randomisation and the use of TPis is becoming the standard operating procedure. This should make the implementation of an enhanced TPi support package and digital nudging relatively straightforward when designing RCTs. These interventions should be evaluated in further trials to achieve a greater sample size for meta-analysis. The costs associated with this intervention have not been formally investigated and a formal cost benefit evaluation would also be a valuable addition. A potential improvement would be assessing further time points to determine the length of time each of these interventions may have an effect for before recruitment fatigue.

3.4.7 Conclusion

An education and support programme targeted at surgical TPis involving a digital education package, 1:1 telephone induction and subsequent support package was effective in increasing recruitment in the first six months of trial commencement. There was no evidence for the effectiveness of the digital nudge intervention in isolation, though, the results show that, when combined with an education programme, it leads to enhanced effectiveness of that programme.

4 A systematic review of deep surgical site infection when antibiotic loaded bone cement is used in patients with a neck of femur fracture treated with a cemented hemiarthroplasty

4.1 Summary

Background

Surgical site infection (SSI) in patients with hip fracture carries significant risks of morbidity and mortality. The use of antibiotic loaded bone cement (ALBC) in patients receiving hip hemiarthroplasties is seen as a potential strategy for reducing the risk of SSI. There is however a lack of evidence synthesis for the use of ALBC in patients with fractured neck of femur injuries.

Aims

This systematic review aimed to review the evidence for the use of plain and antibiotic loaded bone cement on SSI rates in patients receiving a hip hemiarthroplasty for hip fracture.

Methods

Electronic databases including Ovid Medline, Embase, ISI Web of Science, Cochrane CENTRAL, Clinical trials gov and WHO International Clinical Trials Registry Platform (ICTRP) were searched between inception of respective databases and November 9th, 2022. Randomised control trial and non-randomised studies with comparator groups were included. Two investigators independently reviewed studies for legibility and the lead author data extracted and evaluated risk of bias using the Newcastle-Ottawa scale for cohort studies and Cochrane risk of bias tool for RCTs.

Results

The search identified 618 records within which 31 duplicates were removed and one further study was manually added from a protocol of a study identified from searches. 587 studies were reviewed by title and abstract and subsequently nine were identified for full text review. Six studies met eligibility criteria for final inclusion in this review.

Three of the non-randomised studies were of poor quality whilst one was appraised as good. One of RCTs was assessed as having no concerns of bias whilst another had some concerns in the domain of randomisation.

Two studies included compared plain bone cement to low dose single ALBC and showed results favouring ALBC's reduction in SSI. Four studies compared low dose single to high dose dual ALBC and showed mixed results with two studies favouring high dose dual ALBC. There was significant clinical and methodological heterogeneity between the studies.

Conclusions

This review recommends the use of low dose single antibiotic loaded cement for prevention of SSI in patients with hip fractures receiving a cemented hemiarthroplasty. Further high quality RCT evidence in progress needs to be considered and reviewed with existing evidence to determine whether there is any positive effect on SSI prevention from the use of high dose dual ALBC.

4.2 Introduction

Current National Institute for Health and Care Excellence (NICE) guidelines on hip fracture management recommends the use of a cemented prosthesis when surgically treating intracapsular fractures.(NICE 2023; Parker and Cawley 2020). This has been described in detail in (chapter 1.1.1)

Given that the majority of patients with hip fractures are treated surgically (Boulton, Johansen, and Wakeman 2016) and often present with frailty and numerous co-morbidities, there is a significant risk of surgical site infection (SSI) (Roche et al. 2005). In the UK, surgical site surveillance is monitored by the UK Health Security Agency (UK HSA), previously known as Public Health England, however these SSI figures may be underreported (Tanner et al. 2013). The 2022-2023 UK HSA report stated that the SSI rates in hip replacement were 0.5% and in repair of neck of femur were 0.7% (Elgohari and S. Thelwall, T. Lamagni 2014). A systematic review and meta-analysis of 20 UK hip fracture studies reported data from 88,615 patients (Masters et al. 2020). The pooled estimate of infection based on data from 11 of 20 studies (491 infections in 30,740 patients) was 2.1% (95% CI 0.78% to 1.93%). There were 12 studies that reported infection after a hemiarthroplasty with a pooled SSI estimate of 2.87% (95%CI 1.99% to 3.75%). The true rate of SSI is significantly under reported as the national SSI surveillance rate is significantly lower than UK published estimates of infection. Therefore, strategies to reduce SSI in patients who are treated with a hemiarthroplasty after neck of femur fracture may confer significant benefit.

The mortality rate in the population with infected hemiarthroplasty has been shown to be up to 50% therefore the prevention of surgical site infection is a clinical priority to improve outcomes (Guren et al. 2017; Edwards et al. 2008; Noailles et al. 2016). Current standard UK practice includes the use of antibiotic loaded bone cement with no consensus regarding type, dose, or antibiotic content of the cement. The evidence basis for use of antibiotic loaded bone cement in hip fractures is limited but there is mixed clinical evidence regarding a pre-mixed high dose gentamicin and clindamycin bone cement. Some studies have shown a clinically important effect in reducing surgical site infection (Sprowson et al. 2016; Tyas et al. 2018; Savage, McCormick, and Al-Dadah 2019) whilst one large randomised clinical trial showed no difference on deep SSI rate using high dose dual antibiotic loaded bone cement (ALBC) compared to standard of care (Nickil R. Agni et al. 2023).

Published literature on the use of ALBC versus plain bone cement (PBC) for elective hip and knee arthroplasty has mixed conclusions and this had been summarised in a previous chapter (chapter 1.2). However, to my knowledge after preliminary searches on Medline, Cochrane database and PROSPERO

registry, there were no systematic reviews that have been registered or in publication specifically directed towards the trauma population. This group are a distinct population subset in contrast to elective osteoarthritic patients requiring a total hip replacement. There is therefore a need to identify and review the evidence basis for the use of ALBC in patients who have hip fractures. Numerous UK hospitals now also use high dose dual ALBC as standard of care and with the recent WHiTE 8 trial reporting no difference in deep SSI outcome, there is a significant economic burden of using a more expensive cement that has not been shown to be beneficial. This is a comprehensive systematic review of all literature on the research topic up to November 2022.

This systematic review will aim to explore two main objectives:

1. Is low dose single antibiotic loaded bone cement better than plain bone cement at preventing deep infection in patients undergoing a hip hemiarthroplasty for a neck of femur fracture?
2. Is high dose dual ALBC better than single antibiotic loaded cement at preventing deep infection in patients undergoing a hip hemiarthroplasty for a neck of femur fracture?

4.3 Methods

A systematic review was conducted and reported in line with PRISMA 2020 guidance (Page et al. 2021). The study protocol was registered prospectively (PROSPERO CRD42022360341, appendix 7.3.1) on 4th November 2022. This was done to promote transparency and reduce the chance of duplication of the work by any another group whilst conducting the review.

4.3.1 Search strategy

Prior to registering the systematic review, a search was made on the PROSPERO and COCHRANE registers to ensure that the planned systematic review was not being duplicated. Following this, Ovid Medline, Embase, ISI Web of Science, Cochrane CENTRAL, Clinical trials gov and WHO International Clinical Trials Registry Platform (ICTRP) were searched between inception and November 9th, 2022.
The computer-based searches combined free and MeSH search terms and combination of key words related to the intervention (e.g., “antibiotic loaded cement”, “bone cement”, “cemented”, “hip”, “hemiarthroplasty”, “half hip replacement”) and surgical site infection (e.g., “surgical site infection”, “prosthetic joint infection”, “deep infection”, “infection”). The full search strategy for MEDLINE is available in appendix 7.3.2 and this was adapted for the use in other databases listed above.

4.3.2 Study inclusion and exclusion criteria

It was anticipated that there would be limited randomised controlled trial (RCT) evidence for this topic therefore the search was broadened to include study designs other than RCTs to evaluate the best available evidence for this practice.
Studies included were RCTs, quasi-randomised and nonrandomised studies with a control group comparing SSI rate in ALBC to either another concentration of ALBC or PBC. Non-English language studies were also included if suitable translations could be acquired.

Any study without a comparator group and study protocols were excluded. Any study protocol for a RCT that would have met inclusion criteria was investigated further through author contact to determine if publication of the results was due within a reasonable time to be included in this systematic review.

4.3.3 Eligibility Criteria

4.3.3.1 Population

The population involved patients receiving a cemented hip hemiarthroplasty for an intracapsular neck of femur fracture. I included studies with participants receiving all types of cemented hemiarthroplasties designs using any surgical approach and any combination of perioperative

oral/parenteral prophylactic antibiotic therapy. Studies that included cemented hemiarthroplasties for fracture as a subgroup were also included as so long as data could be extracted separately.

Participants receiving elective total hip and total knee replacements and emergency total hip replacements were excluded. Revision cases and surgery in the context of active hip infection were also excluded.

4.3.3.2 Intervention

The intervention was the intraoperative use of ALBC when performing a cemented hemiarthroplasty for an intracapsular neck of femur fracture.

I included studies with any dose and combination of ALBC either in pre-formulated preparations or self-manufactured during surgery.

4.3.3.3 Comparator

Eligible study comparators were a group with differing doses of bone cement to the intervention group; either single ALBC or PBC.

4.3.4 Outcomes

4.3.4.1 Primary outcome

The primary outcome investigated was the rate of deep SSI. I included studies that report follow up of hip hemiarthroplasty patients for infection outcomes. The classification system for deep infection and follow up duration was not specified as to maximise search results.

4.3.4.2 Secondary outcome

The secondary outcomes that were of interest were any validated measure of quality of life, mortality, rates of complication and antibiotic resistance profiles.

4.3.5 Selection of studies

All search results were imported on to specialist systematic review software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. 2023 Available at www.covidence.org).

After duplicated studies were removed, two reviewers, the author of the thesis (NA) and Hariharan Dwarakanathan (HD, orthopaedic senior clinical fellow, Golden Jubilee National Hospital), independently reviewed the titles and abstracts. Eligibility criteria from the protocol was applied to

assess each study for potential full manuscript review. Any disagreement was resolved with discussion and a third senior reviewer used if needed for arbitration. Full manuscripts were obtained for titles and abstracts identified as potentially eligible and reviewed by NA using the same methodology. References for the full manuscripts that were eligible were searched for further studies to be included but no additional studies were added. Two relevant protocols were identified from the search strategy for the WHiTE 8 trial and DAICY trial with the former having completed recruitment and latter still recruiting (N. R. Agni et al. 2021; Mukka et al. 2022). The chief investigator for the WHiTE 8 trial (Matthew Costa) was contacted to request addition of the unpublished study to the systematic review. This full paper was subsequently added to the Prisma study flow diagram (Figure 1). No grey literature or conference abstracts were searched.

4.3.6 Data extraction

I extracted data using a standardised data extraction form (Microsoft Word Version 16.54) and presented information in a 'Characteristics of included studies' (table 36) and 'results' table (table 37). Information extracted included, where available: study type, publication date, geographical location, mean age, intervention, duration of follow-up, infection classification, sample size, number of deep infection events, risk estimates.

4.3.7 Risk of bias assessment

I assessed the risk of bias for each included study, using the Cochrane Risk of Bias 2 (RoB2) tool for randomised control trials and the nine-star validated Newcastle-Ottawa Scale (NOS) for cohort studies (Higgins and Altman 2008; Sterne et al. 2019).

The RoB2 was developed using a consensus method and is refined from the original Cochrane Risk of Bias tool to improve assessment of risk of bias and to address user feedback on limitations of application. This tool is easy to apply to RCTs and widely used in Cochrane reviews with high quality guidance on implementation of the measure to studies. The RoB2 tool classifies risk of bias based on five domains. These include bias from the randomisation process, deviations from intended intervention, missing outcome data, outcome measurement and selection of reported results.

There is no gold standard when choosing a tool for non-randomised studies however the two recommended by the Cochrane handbook based on a systematic review by Deeks et al. (Deeks et al. 2003) were the Downs and Black instrument and the NOS tool. The NOS is easier to apply and uses

three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest.

4.3.8 Data synthesis

A qualitative narrative synthesis was undertaken and reported in line with PRISMA and SWiM guidelines (Campbell et al. 2020; Page et al. 2021), which are intended to be used in systematic reviews lacking data amenable to meta-analysis. This is a 9-point check used in complement with the PRISMA 27-point check list to improve reporting of systematic reviews.

A table of study characteristics and results were created and summarised (table 36 and table 37). Risk estimates (odds ratios) were used as the common measure of association across studies and were calculated for studies that reported counts in isolation or where odds ratio was not presented. This allowed for comparisons between study outcomes in a standardised way.

Clinical and methodological heterogeneity was considered to determine whether studies could be pooled, and subsequent meta-analysis could be undertaken. Forrest plots were also created with the intention to present either individual or pooled estimates depending on the level of heterogeneity between studies.

4.4 Results

4.4.1 Search Results

The search strategy retrieved 618 records and is summarised in a PRISMA flow diagram (figure 19). Thirty-one records were duplicates and removed and one further study was manually added from a protocol of a study (N. R. Agni et al. 2021) identified from searches. The protocol had been published but the full trial was pre-publication. Two independent reviewers (NA and HD) screened 587 records by title and abstract resulted in 578 exclusions. Nine records were identified for full text review with 95% agreement between reviewers. HD identified 12 further studies for full review however this discrepancy between reviewers was discussed and agreed without the need for a third reviewer for resolution. No further studies were added after discussion as they did not meet the review inclusion criteria.

After full text review of the nine studies, six of these met eligibility criteria. Three of the full texts were published protocols for RCTs of which one was linked to an already published study (A. P. Sprowson et al. 2016); one was in reference to an RCT that was pre-publication (Nickil R. Agni et al. 2023); one was still recruiting to the linked trial (Mukka et al. 2022). The latter DAICY protocol had a timeline outside the completion of this systematic review with an estimated completion date of 2027.

There were 6 studies finally included in this systematic review (Aedo-Martín et al. 2020; Sanz-Ruiz et al. 2017; Tyas et al. 2018; Savage, McCormick, and Al-Dadah 2019; Sprowson et al. 2016; Nickil R. Agni et al. 2023).

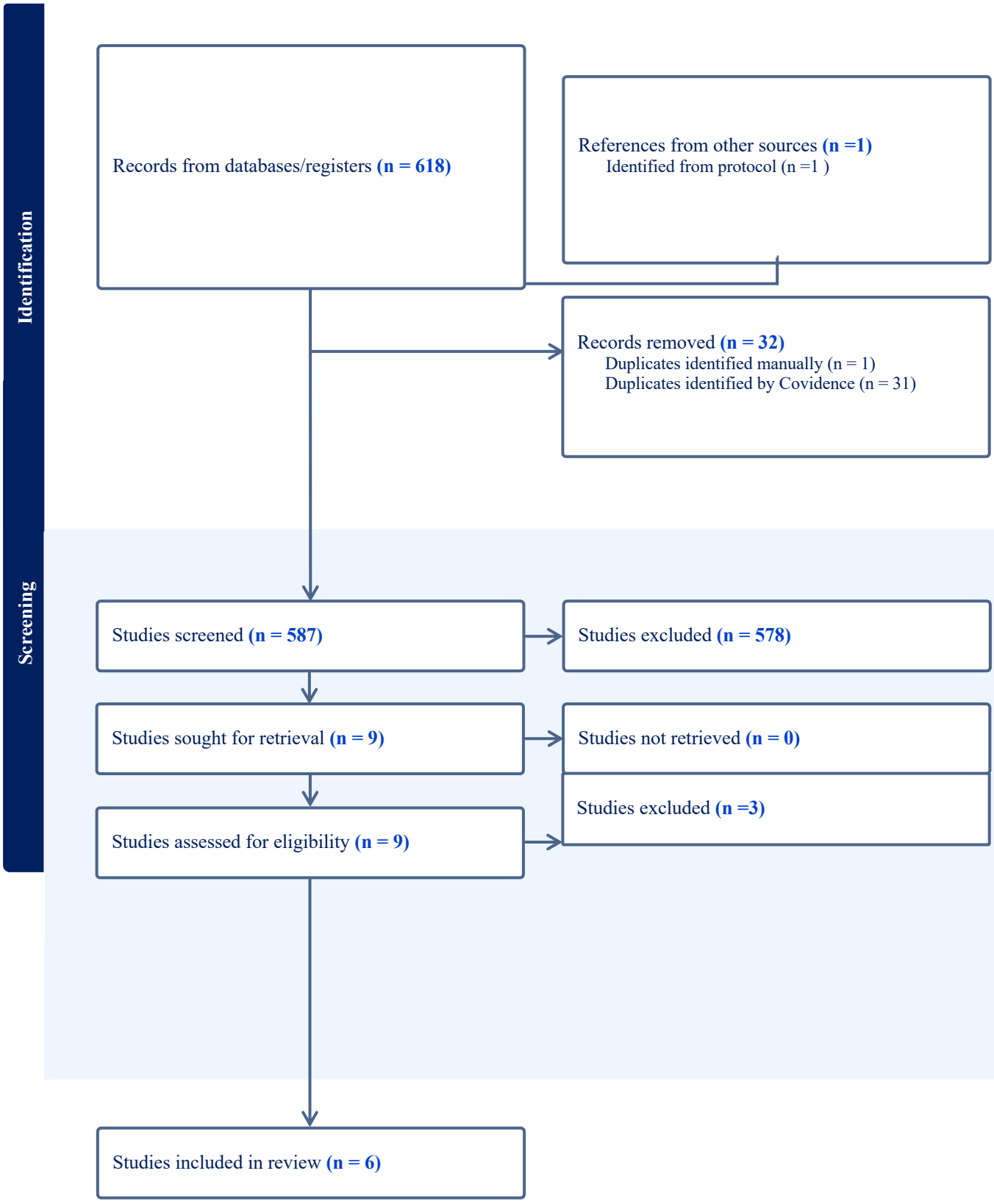


Figure 19: PRISMA flow chart of systematic review study selection

4.4.2 Study Characteristics

There were two main aims of this study:

1. Is low dose single ALBC better than PBC at preventing deep infection in patients undergoing a hip hemiarthroplasty for a neck of femur fracture?
2. Is high dose dual ALBC better than single antibiotic loaded cement at preventing deep infection in patients undergoing a hip hemiarthroplasty for a neck of femur fracture?

Two studies were identified relevant to question 1 (Aedo-Martín et al. 2020; Sanz-Ruiz et al. 2017) and 4 studies were identified relevant to question 2 (Tyas et al. 2018; Savage, McCormick, and Al-Dadah 2019; Sprowson et al. 2016; Nickil R. Agni et al. 2023). They key characteristics of each study is summarised below and in table 36, with further detail with regards to results summarised in table 37.

4.4.2.1 Study summaries

Six studies were identified with four from the United Kingdom and two from Spain published between the year 2016 and 2023. Three were retrospective cohort studies, one mixed retrospective and prospective, one quasi randomised trial and one randomised control trial. Samples ranged from 206 to 4936 and in total four different classifications of deep infection for utilised. A summary of each study is outlined below.

Aedo-Martin et al (2019)

This retrospective cohort study from a single hospital in Madrid was published in 2019 with a sample size of 241 patients. The study investigated patients who underwent hip hemiarthroplasty due to a subcapital fracture between 2011 and 2017. They excluded patients who died within the first 30 days of surgical intervention and those who had pathological fractures.

Patients received prophylactic para-enteral antibiotics at the time of surgery. Cefazolin (Vancomycin if allergic) was given, one dose before surgery and three doses after. The control group used CEMEX®(TECRAS SPA, Italy) which is an antibiotic free bone cement whilst the intervention group received Palacos®R + G (Heraeus Medical GmbH, Germany) containing 0.5g of Gentamicin antibiotic. The primary outcome was the development of acute or late infection using the Musculoskeletal Infection Society 2011 criteria (Parvizi et al. 2011). Secondary outcome for this study was a cost benefit analysis of each investigated group.

241 patients were identified with 94 patients in the ALBC group and 147 patients in the plain bone cement group. The outcome results have been summarised in table 37. The authors conclude that

antibiotic loaded bone cement is protective in preventing late infection in patients receiving a hemiarthroplasty for a fractured neck of femur.

Sanz-Ruiz et al (2017)

This retrospective cohort study from a single hospital in Madrid was published in 2016 (Sanz-Ruiz et al, 2017). The population investigated were those receiving cemented partial hip replacements, total hip replacements and total knee replacements from 1st January 2009 to 31st December 2012. Cemented implants were selected in hip arthroplasty patients when poor quality of bone was observed.

From 1st Jan 2009 to 31st Dec 2010 a cement without antibiotics was used (not identified). From 1st Jan 2011 to Dec 31st, 2012, Palacos®R + G (Heraeus Medical GmbH, Germany) containing 0.5g gentamicin was the cement of choice. Diagnosis of infection was based on Musculoskeletal Infection Society 2011 criteria (Parvizi et al. 2011) and minimum follow up was 2 years. There was no description of prophylactic para-enteral antibiotics at the time of surgery. Primary outcome was the rate of infections in each group whilst secondary outcomes also included assessment of cost-benefit ratio of the use of ALBC.

2518 patients were included in the study of which 663 had partial hip replacements. 70.4% of these were cemented (469 cases) in contrast to 91.8% of total hip replacements that were uncemented. Results are summarised in table 37. The authors conclude that the use of antibiotic loaded bone cement is protective in preventing prosthetic joint infection in hip arthroplasty.

Tyas et al (2018)

This retrospective cohort UK study was conducted in a single NHS foundation trust made up of two hospitals. The population included were those receiving hemiarthroplasties after a neck of femur fracture between April 2008 and December 2014. All patients with infections in the period were detected via the trusts SSI surveillance database which is routinely collected data.

All patients received prophylactic teicoplanin and gentamicin (aztreonam in if there was renal impairment) antibiotics pre-operatively. The cements used in each group for comparison was Palacos®R + G (Heraeus Medical GmbH, Germany) containing 0.5g gentamicin and Copal®G + C (Heraeus Medical GmbH, Germany) containing 1g gentamicin and 1g clindamycin. Minimum follow up duration was not stated but Public Health England definitions of infection were used. The outcomes

of interest were the rate of infection, causative organisms, and antibiotic resistance profiles in each group.

1941 patients were identified with 681 in the Palacos®R + G group and 1260 in the Copal®G + C group. Results are summarised in table 37.

Savage et al (2019)

This retrospective study was conducted in a single UK district general hospital. The population contained all patients with neck of femur fractures who went on to have a cemented arthroplasty including both partial and total hip replacements. There is no mention of the timeline in which this study was conducted. The population data was extracted from the National Hip Fracture Database (NHFD) and Public Health England definitions of deep SSI were used for up to 1 year after surgery.

All patients received prophylactic teicoplanin and gentamicin unless allergic. The cements used in each group for comparison was Palacos®R + G (Heraeus Medical GmbH, Germany) containing 0.5g gentamicin and Copal®G + C (Heraeus Medical GmbH, Germany) containing 1g gentamicin and 1g clindamycin. The data for the Palacos R+G group was collected retrospectively whilst Copal G+C was collected prospectively. Primary outcome was differences in deep SSI rates between groups whilst secondary outcome was difference in superficial SSI between groups.

206 patients were included in the study of which 180 had cemented hemiarthroplasties. Within this group 95 had Palacos R+ G and 85 had Copal G+C. Results are summarised in table 37. The authors concluded that the use of high dose dual antibiotic loaded cement led to lower deep infections in those receiving hemiarthroplasties after a neck of femur fracture.

Sprowson et al (2016)

This study has been described as a quasi-randomised clinical trial and was published in. It is a two hospital (single NHS foundation trust), two arm, patient and assessor blinded trial with group treatment allocation. The population were patients over the age of 18 presenting with hip fracture requiring a cemented hemiarthroplasty between May 2008 and November 2012. Individual randomisation was not carried out due to lack of local support but allocation to treatment group was based on the date that surgery was performed providing one treatment at each centre for the whole calendar month. The allocation to treatment group was then switched to the alternate group each subsequent month with the aim of having comparable groups.

The cements used in each group for comparison was Palacos®R + G (Heraeus Medical GmbH, Germany) containing 0.5g gentamicin and Copal®G + C (Heraeus Medical GmbH, Germany) containing 1g gentamicin and 1g clindamycin. Prophylactic antibiotics included para-enteral gentamicin 4.5mg/kg prior to February 2009 but this was switched to Teicoplanin 400mg and Gentamicin 3mg/kg after to reduce the risk of acute renal failure.

The primary outcome measure was deep SSI based on definitions of SSI by the Health Protection Agency (NICE 2011). Patients were followed up for SSI to one year post surgery. Secondary outcome measures included superficial SSI rates, mortality, length of stay, Clostridium difficile infections and complication. The sample size was calculated to detect a decrease in rate of deep SSI from 4% to 1% for a two-sided 5% significance and 80% power. 848 patients were entered into the trial with 448 allocated to Palacos R+G and 400 to Copal G+C. Results are summarised in table 37. The authors concluded that the use of high dose dual antibiotic loaded cement led to lower deep infections in those receiving hemiarthroplasties after a neck of femur fracture.

Agni et al (2023)

This randomised clinical trial was published in 2023. This is a multi-centre, multi-surgeon, parallel, two-arm, pragmatic randomised clinical trial embedded in the World Hip Trauma Evaluation. 26 UK recruiting trusts were involved and the population was patients over the age of 60 with intracapsular hip fractures requiring a cemented hemiarthroplasty between August 2018 and August 2021.

Patients were randomly assigned in a 1:1 ratio to receive either Palacos®R + G (Heraeus Medical GmbH, Germany) containing 0.5g gentamicin or Copal®G + C (Heraeus Medical GmbH, Germany) containing 1g gentamicin and 1g clindamycin. All hospitals had their own regimen for perioperative antibiotics and this data was not collected.

The primary outcome was deep SSI at 90 days post-randomisation as defined by the Centers for Disease Control and Prevention classification (National Healthcare Safety Network and US-CDC 2023). Secondary outcomes included antibiotic use, quality of life, mortality, complications, mobility, discharge to home and antibiotic resistance patterns. The sample size was calculated to detect a decrease in rate of deep SSI from 3% to 1% for a two-sided 5% significance and 90% power. 4936 patients were randomised into the trial with 2453 randomised to Palacos R+G and 2483 to Copal G+C. Results are summarised in table 37. The authors concluded that there was no advantage in using high

dose dual antibiotic loaded cement for the prevention of deep infection in patients receiving a hemiarthroplasty in a neck of femur fracture.

Table 35: Characteristics of included systematic review studies

Author (year) & Country	Title	Population	Intervention	Comparator	Study Design	Sample size
Aedo-Martin et al (2019) Spain	Periprosthetic infection in elderly patients treated with hemiarthroplasty of the hip following intracapsular fracture. Should be use antibiotic-loaded bone cement?	Patients admitted to one hospital in Madrid (Spain) between 2011 and 2017. Inclusion of partial hip (hemiarthroplasty) for hip fracture. Exclusion of anyone dying int the first 30 days post op	Low dose single ALBC (Palacos R+G)	Cement without antibiotic (CEMEX)	Retrospective cohort	241 patients; 147 received CEMEX, 94 received Palacos R+G
Sanz-Ruiz et al (2017) Spain	Is the Commercial Antibiotic-Loaded Bone Cement Useful in Prophylaxis and Cost Saving After Knee and Hip Joint Arthroplasty? The Transatlantic Paradox	Patients admitted to one hospital in Madrid (Spain) between 1st January 2009 and December 31st, 2012. Inclusion of total hip, partial hip, and total knee arthroplasties	Low dose single ALBC (Palacos R+G)	PBC	Retrospective cohort	469 patients; 248 received PBC, 221 received Palacos R+G
Tyas et al (2018) UK	Antibiotic resistance profiles of deep surgical site infections in hip hemiarthroplasty; comparing low dose single antibiotic versus high dose dual antibiotic impregnated cement	*Patients needing hip hemiarthroplasties admitted to one UK NHS foundation trust (two hospitals) between April 2008 and December 2014	High dose dual ALBC (Copal G+C)	Low dose single ALBC (Palacos R+G)	Retrospective cohort	1941 hemiarthroplasties: 681 received Palacos R+G, 1260 received Copal G+C
Savage et al (2019) UK	Arthroplasty infection rates in fractured neck of femur: single vs dual antibiotic cement	Patients admitted to one UK NHS hospital. All cemented arthroplasties were included including partial and total.	High dose dual ALBC (Copal G+C)	Low dose single ALBC (Palacos R+G)	Mixed retrospective and prospective cohort	206 patients: 95 received Palacos R+G, 85 received Copal G+C
Sprowson et al (2016) UK	The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip	*Patients needing hemiarthroplasties admitted to one UK NHS foundation trust (two hospitals) between May 2008 and November 2012	High dose dual ALBC (Copal G+C)	Low dose single ALBC (Palacos R+G)	Quasi randomised control trial	848 hemiarthroplasty patients: 448 received Palacos R+G, 400 received Copal G+C
Agni et al (2023) UK	High-dose dual-antibiotic loaded cement for hip hemiarthroplasty in the UK (WHiTE 8): a randomised controlled trial	Patients admitted to 26 NHS hospitals between August 2018 and August 2021	High dose dual ALBC (Copal G+C)	Low dose single ALBC (Palacos R+G)	Randomised control trial	4936 patients; 2453 received Palacos R+G, 2483

Antibiotic loaded bone cement (ALBC); Plain bone cement (PBC); *Both studies used the same population within the same UK NHS foundation trust

Table 36: Results of included systematic review studies

Author (year)	Outcomes investigated	Mean age	Classification of infection	Follow up	Deep SSI rates	Other outcomes	Risk of deep SSI (odds ratio)
Aedo-Martin et al (2019)	SSI rates, contributors to infection, cost analysis	not reported	MSIS classficiation 2011	Not clearly defined, >3 months	Total: PBC 28/147 (19.0%), Palacos R+GG 8/94 (8.51%). Acute <3months: PBC 8/147 (5.44%) vs Palacos R+G 4/94 (4.3%). Late >3months: PBC 20/147 (13.6%) vs Palacos R+G 4/94 (4.3%)	Cost was 24,205 EUR per patient in acute infection and 35,746 EUR in late infection. Mean patient costs were 14,127.54 EUR in ALBC group and 17.632.81 EUR in PBC	Overall Odds ratio 0.4 (95% Ci 0.17 - 0.91). Acute < 3 months OR 0.77 (95% CI 0.23 - 2.64). Chronic >3 months OR 0.28 (95% CI 0.09 - 0.85)
Sanz-Ruiz et al (2016)	SSI rates, causal organisms, Costs analysis	Palacos R+G group 81.4, PBC group 81.1	MSIS classficiation 2011	Minimum follow up 2 years	5/221 (2.3%) infections after Palacos R+G vs 21/248 (8.5%)infections PBC	Global decrease in PPI from 4.3% to 1.8% (RR 0.42, CI 0.25 - 0.7, p=0.001). Knee arthroplasty decrease in PPI from 3.3% to 1.3% (RR0.37; CI 0.16-0.87, p=0.019). Cemented Total Hip Arthroplasty PPI decrease from 7.1% to 2.8% (RR0.37; CI 0.02-6.38, p=0.95). Cost saving of 2514 EUR per patient using ALBC after cemented hip arthroplasty	*Calculated: OR 0.25 , 95% CI (0.09, 0.68)
Tyas et al (2018)	SSI rates, infetion organisms, antibiotic susceptibilty patterns	not reported	PHE definition	Not stated	38/1941 infections, 23 Palacos R+G (3.4%) vs 15 Copal G+C (1.2%)	Polymicrobial infection 43.48% Palacos R+G vs 53.33% Copal G+C (p=0.641). Staph epidermidis 8.7% Palacos R+G vs 33.33% Copal G+C (P=0.001). No difference in Deep SSI resistance to Clindamycin (p=0.134), Gentamicin (p=0.305) or both (p=0.643)	*Calculated: OR 0.34 , 95% CI (0.18,0.67)
Savage et al (2019)	SSI rates	Palacos R+G 83. Copal G+C 84	PHE definition	Not stated	Palacos R+G 3/95 (3.2%) vs Copal G+C 0/85 (0%)	Superficial SSI rate of 4/95 (4.2%) in Palacos R+G, 0/95 (4.2%) in Copal G+C	*Calculated (OR 0.15, 95% CI (0.01, 3.04). Haldane-Anscombe correction
Sprowson et al (2016)	Deep SSI, Superficial SSI, mortality, length of stay, Clostridium difficile infections and complications	Palacos R+G 83.34 Copal G+C 82.96	HPA definiton	Deep SSI at 30 days and 1 year	Palacos R+G 13/376 (3.5%) vs Copal G+C 4/360 (1.1%)	Combined deep and superficial SSI: Palacos R+G 20/376 (5.3%) vs Copal G+C 6/360 (1.7%). Death: Palacos R+G 60/390 (15.4%) vs Copal G+C 56/347 (16.1%). Length of stay: no difference between groups. Critical care stay:Palacos R+G 19/404 (4.7%) vs Copal G+C 2/384 (0.5%) Clostridium difficile infection: Palacos R+G 5/359 (1.37%) vs Copal G+C 9/341 (2.57%) Surgical and medical complications: no difference between groups	Adjusted Intention to treat: 0.31, 95% CI 0.09 to 0.88. Adjusted Per Protocol: 0.33, 95% CI 0.09 to 0.95
Agni et al (2023)	Deep SSI, antibiotic use, quality of life, mortality, complications, mobility, discharge to home, antibiotic reisstnace	Palacos R+G 83.8 Copal G+C 83.9	CDC critiera for Deep SSI (90 days)	Deep SSI at 90 days. Secondary outcones 120 days	Primary analysis: Palacos R+G 38/2187 (1.7%) vs Copal G+C 27/2219 (1.2%), Per protocol: Palacos R+G 35/2020 (1.7%) vs Copal G+C 23/1999 (1.2%), As treated: Palacos R+G 38/2115 (1.8%) vs Copal G+C 24/2185 (1.1%)	Antibiotic use: No difference between groups EQ-5D-5L: No difference between groups Mortality: No difference between groups Complications: No difference between groups Mobility: No difference between groups Discharge to home: No difference between groups Resistance to antibiotics: No difference between groups	Primary: 1.43, 95% CI 0.87 to 2.35, Per protocol 1.52, 95% CI 0.89 - 2.58, As treated: 1.6, 95% CI 0.95 - 2.71 Calculated reverse odds ratio Primary: 0.70, 95% CI 0.43 to 1.15, Per protocol 0.66, 95% CI 0.39 to 1.12, As treated: 0.63, 95% CI 0.37 to 1.05

Musculoskeletal infection society (MSIS); Public Health England (PHE); Health Protection Agency (HPA); Centers for Disease Control and Prevention (CDC); *Calculated odds ratio from raw figures as this risk estimate was not provided in original study publication

4.4.3 Risk of bias

Each of the four studies was quality assessed using the Newcastle Ottawa Scales. Overall, three out of four of the retrospective studies were scored as 'poor' and one was scored as 'good'. Scores ranged from three to eight and of interest only two studies scored for comparability between investigated groups. All studies scored in the domain of Selection for 'ascertainment of exposure' and 'outcome of interest' and in the domain of outcome for 'assessment of outcome'. The differences in scoring between the studies is summarised in table 38 and further summaries on individual study scores are summarised in appendix 7.3.3 and 7.3.4.

Table 37: Newcastle Ottawa Scale assessments

Study	Selection				Comparability	Outcome			*Overall
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Follow up long enough for outcome to occur	Adequacy of follow up	
Aedo-Martin et al (2019)			★	★	★★	★			5 Poor
Sanz-Ruiz et al (2016)		★	★	★	★★	★	★	★	8 Good
Tyas et al (2018)	★	★	★	★		★			5 Poor
Savage et al (2019)			★	★		★			3 Poor

*Good quality: Three or four stars in selection domain AND one or two stars in comparability domain AND two or three stars in outcome/exposure domain. Fair quality: two stars in selection domain AND one or two stars in comparability domain AND two or three stars in outcome/exposure domain. Poor quality: zero or one star in selection domain OR zero stars in comparability domain OR zero or one star in outcome/exposure domain.

There were two studies assessed using the Cochrane Risk of Bias 2 tool. Whilst the study by Sprowson et al (2016) is described as a quasi-randomised control trial the Cochrane Risk of Bias 2 tool was a better fit for assessing risk of bias in evaluated domains rather than the Newcastle Ottawa Scale. These are summarised in figure 21 and figure 22.

Randomised control trials report several outcomes for which multiple risk of bias assessment would be needed to carry out. Considering the objective of this systematic review, only the primary outcome of deep surgical site infection outcome was considered for risk of bias assessment. There was some concern in the FHIT study (Sprowson et al. 2016) regarding bias from the allocation process. Individual patients were not randomised to an intervention but rather, there was cluster allocation of centres to an intervention that alternated each subsequent month. However as noted by the author most of the neck of femur fracture (95%) were operated on within 48 hours of presentation due to the monetary incentives of the 'Best practice tariff' (Alim and Nordin 2023) and thus subverting the cluster allocation

would not have likely occurred. Therefore, this domain was scored as 'some concerns' rather than 'high' risk.

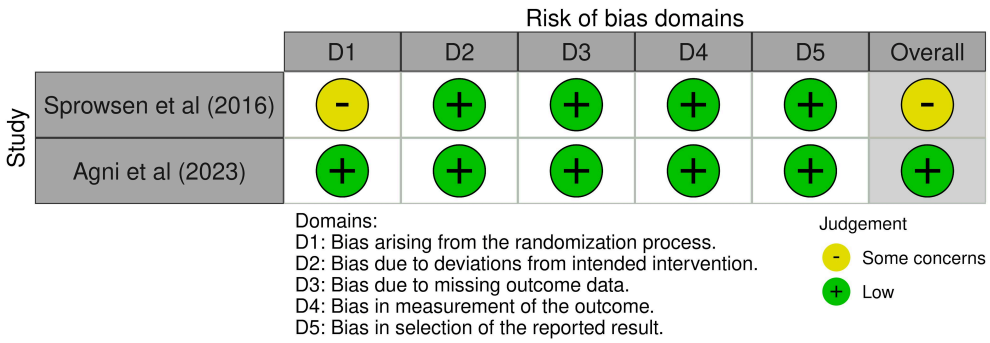


Figure 20: Traffic light plots of the domain-level judgements

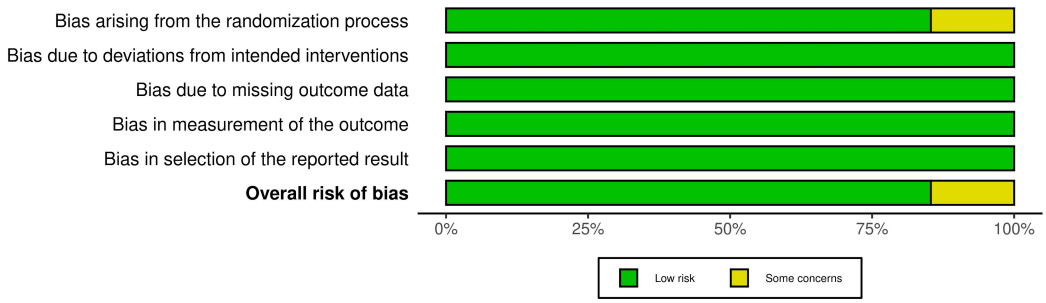


Figure 21: Weighted bar plots of the distribution of risk-of-bias judgements within each bias domain

4.4.4 Plain bone cement vs antibiotic loaded bone cement

Two retrospective cohort studies (Sanz-Ruiz et al. 2017; Aedo-Martín et al. 2020), investigated this intervention and reported similar odds ratio in favour of ALBC for preventing deep SSI. The odds ratios were OR 0.25 (95% CI 0.09 to 0.68) and 0.4 (95% CI 0.17 to 0.91) and have been shown on a forest plot without a pooled estimate (figure 23). A pooled estimate was not calculated due to significant clinical and methodological heterogeneity, and this is explored further below. Secondary outcomes in both studies explored the cost savings per patient from using ALBC and is summarised in table 37. This secondary outcome has not been explored further in this systematic review.

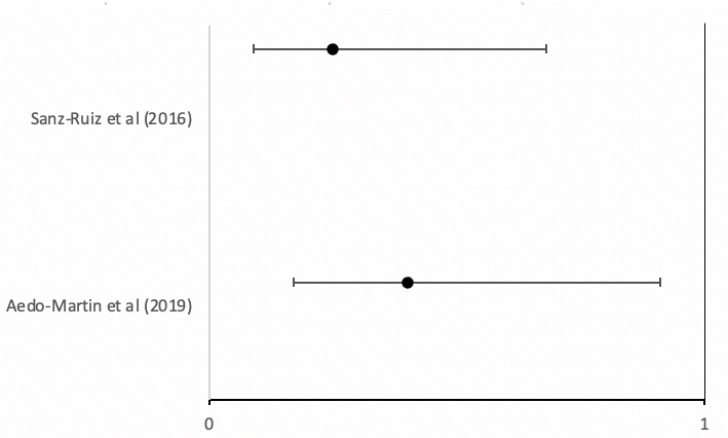


Figure 22: Forest plot of studies involving PBC vs ALBC. Less than one favours antibiotic loaded bone cement.

The clinical heterogeneity of the studies was assessed. Patient level comparisons between the studies were made. Both were Spanish studies using the local population with significant differences in representativeness of the population. Sanz-Ruiz et al (2016) used a population not representative of all hip fractures in their community as only those with poor quality bone were given cemented partial hips. Poor bone is often a proxy for frailer patients with increased co-morbidities. Aedo-Martin (2020) used a sample of 241 patients from January 2011 -January 2017 however, it is not clear or reported whether this included all the patients in this period and what the standard of care was at the hospital i.e., cemented or uncemented hips. It is therefore not representative of the hip fracture population. Additionally, any patient dying within the first 30 days was excluded with no rationale for this decision. Sample size was different with 241 vs 469 patients in Aedo-martin et al (2020) and Sanz-Ruiz et al (2016) respectively.

Aedo-Martin (2020) does not clearly report each groups mean age but rather the percentage of patients >80 years old was 81.6% in plain cement group and 73.4% in the ALBC group. Mean age in Sanz-Ruiz et al (2016) was 81.1 years and 81.4 years respectively for plain cement and ALBC groups. Co-morbidities were only reported in Aedo-Martin (2020) with history of medical risks for developing infection reported as 25.9% in plain cement group and 39.4% in the ALBC group.

Intervention level comparisons showed that both studies used the same brand of ALBC (Palacos R+G) and so were comparable. Prophylactic antibiotics were reported to be given in Aedo-Martin (2020) but there is no statement in Sanz-Ruiz et al (2016).

The methodological quality of Sanz-Ruiz et al (2016) was scored ‘good’ and Aedo-Martin (2020) was scored poor (table 38). Methodological heterogeneity assessment showed the same definitions for

diagnosing deep infection were used (MSIS criteria 2011). Minimum follow up was clearly defined as 2 years in Sanz-Ruiz et al (2016) but could only be implied to be 3-months in Aedo-Martin (2020) as follow up was not clearly stated. For deep SSI differences odds ratio was reported in Aedo-Martin (2020) but relative risk was reported in Sanz-Ruiz et al (2016) therefore odds ratio was calculated and presented to allow comparison between studies (table 37).

4.4.5 Low dose single ALBC vs High dose dual ALBC

Four studies reported outcomes for this intervention, two cohort studies, one quasi-randomised trial and one RCT (Tyas et al. 2018; Savage, McCormick, and Al-Dadah 2019; Sprowson et al. 2016; Nickil R. Agni et al. 2023).

All four studies reported deep SSI rates in both intervention and comparator groups (table 37). Sprowson et al (2016) and Tyas et al (2018) both report favourability towards high dose dual ALBC with odds ratio of 0.31 (95% CI 0.09 to 0.88) and OR 0.34 (95% CI 0.18 to 0.67) respectively. Savage et al (2019) only report raw data in groups with 4/95 deep infections (3.2%) in low dose single ALBC and 0/85 (0%) in high dose dual ALBC groups. The Haldane – Anscombe correction method was used to calculate odds ratio due to the high dose dual ALBC group having a 0% SSI rate. Calculated odds ratio, OR 0.15 (95% CI 0.01 to 3.04) shows a large confidence interval that does not support the authors conclusion of a positive effect of high dose dual ALBC on reducing deep SSI. Agni et al (2023) reported no difference between groups with calculated odds ratio being 0.70 (95% CI 0.43 to 1.15) for ease of comparison. The forest plot for the studies is represented in figure 24 with individual estimates rather than pooled due to the heterogeneity between studies discussed below.

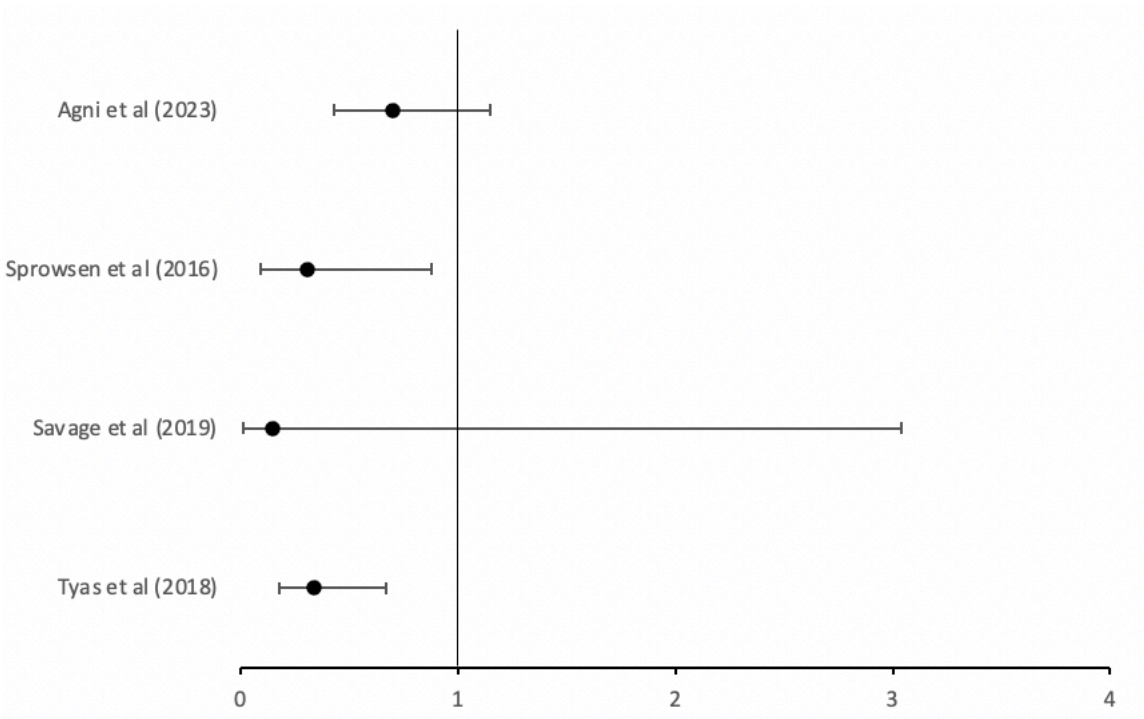


Figure 23: Forest plot of studies involving low dose single ALBC vs high dose dual ALBC. Less than one favours high dose dual antibiotic loaded bone cement

Quality of Life is not reported in Sprowson et al (2016), Tyas et al (2018) and Savage et al (2019). Agni et al (2023) used EQ-5D-5L and show no difference between the two groups, adjusted for age, sex and centre as a random effect with the difference being -0.008 (95%CI, -0.024 to 0.008).

Mortality is reported as no different between intervention groups (p=0.858) in Sprowson at al (2016) with a rate of 15.4% in the single ALBC group and 16.1% in the dual ALBC group. Agni et al (2023) reported mortality of 20.7% in the single ALBC group and 19.8% in the dual ALBC group with an adjusted treatment difference of 1.06 (95%CI 0.92 to 1.23).

Participants with one or more complication was reported in Sprowson et al (2016) at 35.26% in the single ALBC group and 37.71% in the dual ALBC group. Agni et al (2023) also reported 38.9% and 39.5% respectively. Neither study showed statistical differences between groups.

Antibiotic resistance was reported by Tyas et al (2018) and Agni et al (2023). Neither study reported differences of resistant infections to either of the antibiotics (gentamicin or clindamycin) used in the high dose dual ALBC group when a confirmed deep infection occurred.

Clinical heterogeneity was assessed for the four studies. Heterogeneity at patient level showed similar patient ages in three studies (Savage, McCormick, and Al-Dadah 2019; Nickil R. Agni et al. 2023; Sprowson et al. 2016) but no reported mean age in one study (Tyas et al. 2018).

The population included in three studies were comparable (Tyas et al. 2018; Sprowson et al. 2016; Nickil R. Agni et al. 2023) as they were representative of the population of hip fractures by including all presenting hip fractures in a determined study period. One study (Savage, McCormick, and Al-Dadah 2019) reported 206 patients in their study but there was no statement regarding the data collection period and whether this sample was representative of the hip fracture population. Both trials (Sprowson et al. 2016; Nickil R. Agni et al. 2023) report co-morbidity data and show no difference between groups, but the cohort studies did not report this data therefore comparisons between groups and studies are difficult to make. There are differences in sample sizes with the smallest study having only 206 patients (Savage et al 2019) and the largest having 4936 patients (Agni et al 2023). The sample size of hip fracture used in Tyas et al (2018) was 1941 patients and includes those used in Sprowson et al (2016) as both studies involved the same NHS Hospital Foundation Trust with overlapping study periods.

Interventional level comparisons show the same cement being used in both single and dual ALBC groups between studies. All patients in studies also received prophylactic antibiotics in line with local hospital recommendations.

Methodological heterogeneity with regards to study type has been presented in table 36. The quality of both cohort studies scored low on the NOS and were categorised as poor studies (Savage, McCormick, and Al-Dadah 2019; Tyas et al. 2018). The quality as assessed by the Cochrane RoB2 tool only showed ‘some concern’ for one domain (bias in randomisation) for Sprowson et al (2016) whilst Agni et al (2023) showed ‘Low Risk’ in all domains. The two trials have different methodologies in randomisation with Agni et al (2023) using patient level randomisation 1:1 group ratio with variable block sized allocation sequence stratified by centre. Sprowson et al (2016) used a cluster allocation method which was alternated monthly and thus is not true randomisation. The authors also did not acknowledge this in their sample size calculation. This would have potentially led to inaccurate results as cluster randomised trial generally need much greater sample sizes for statistical analysis (Hemming and Taljaard 2023).

The definition of SSI is not consistent between studies. Two use the Public Health England definition (Tyas et al. 2018; Savage, McCormick, and Al-Dadah 2019), one used the Health Protection Agency definition (Sprowson et al. 2016) and one used the CDC criteria (Nickil R. Agni et al. 2023). Savage et al (2019) and Tyas et al (2018) do not define minimum follow up period but the SSI definition of Public Health England used are follow up at up to one year so we can only assume that this follow up period was adhered to. The methodology for infection data collection is different between studies. Tyas et al (2018) used routinely collected in-hospital surveillance data whilst Savage et al (2019) performed a clinical note review of each patient to determine any readmission positive microbiology samples from the hip. Sprowson et al (2016) had individual patient reported data at 30 days collected by research nurses. From 30 days to 1year monitoring was based on clinical reporting, patient reporting and readmissions monitored by the trusts SSI team. Agni et al (2023) reported 90-day deep infection rates and other secondary outcomes with 120-day telephone interviews with participants or their carers if participants lacked capacity.

4.5 Discussion

4.5.1 Summary

This systematic review reports a comparison in deep SSI rates between plain bone cement and low dose single ALBC in hip fracture receiving a partial hip. It shows weak support for the use of low dose single ALBC in hip fractures from the two included cohort studies. There was significant patient level clinical heterogeneity between the studies and numerous biases arising from selection and outcome assessments of patients, which did not allow for grouping results together for meta-analysis. Secondary outcomes investigated by this review were not applicable to these studies either.

The systematic review also reports a comparison in deep SSI rates between low dose single ALBC and high dose dual ALBC in hip fractures receiving a partial hip. There is mixed evidence on the use of high dose dual ALBC with two cohort study and one quasi randomised trial conclusions favouring the intervention (Tyas et al. 2018; Savage, McCormick, and Al-Dadah 2019; Sprowson et al. 2016). However, Savage et al (2019) did not report any statistical analyses in their paper and when odds ratios and confidence intervals were calculated from raw data it was clear that as the confidence interval on the forest plot crossed 1 (figure 24) there was insufficient evidence to support the authors conclusions. Agni et al (2023) was the only well conducted randomised clinical trial in the systematic review and showed no difference between intervention groups thus supporting the continued used of low dose single ALBC. Secondary outcomes of interest within this study including quality of life indicators, mortality, complications, and antibiotic resistance also showed no differences.

4.5.2 Definitions of infection

In the six studies included in this systematic review there were four different classifications of deep SSI that were used. These included MSIS 2011, CDC definitions, HPA definitions and PHE definitions which are all formally recognised diagnostic systems (Parvizi et al. 2011; Horan, Andrus, and Dudeck 2008; NICE 2011; Health England 2016). This methodological heterogeneity makes comparisons between studies challenging as absolute SSI values may differ when different classification systems are applied. The SSI rate in the four UK studies for low dose single ALBC ranged from 1.7 to 3.5% with the RCT (Agni et al 2023) showing the lowest rate of SSI. Inconsistencies and varied classifications of deep SSI have also been reported in a systematic review and meta-analysis of UK SSI after hip fracture surgery (Masters et al. 2020). The authors found that in 20 studies included, seven used formally recognised systems, six failed to give a definition of infection and the remainder used their own definitions.

4.5.3 Primary outcome data collection

There are key differences in how primary outcome data was collected that may have affected the detected rates of infection. Sprowson et al (2016) followed up each patient post-surgery at 30 days and then relied on routine surveillance within the NHS trust for data on readmission up to one year. They also excluded all deaths within the first 30 days and thus acknowledge that some of these patients may have had a contributary SSI resulting in an under-reporting of the true SSI rate. The same population were included, and the timeline extended to include more patients in Tyas et al (2019). SSI data for the patients was retrieved via the NHS trusts' SSI surveillance database and thus forms a local data capture of patients re-presenting to the same hospital. It would not capture patients who may have migrated or presented to different surrounding hospitals and once again may be an underestimate.

Savage et al (2019) performed a note review on each patient in the sample looking for readmission and microbiology samples. This would, once again, lead to a potential underestimate as patients presenting with SSI to another hospital would not be captured with this method of data collection. Agni et al (2023) collected primary outcome data via telephone interview at 120 days from participants or their carer. Potential and confirmed infections were then followed up with the hospital in which their surgery was performed for further specific information. This was the only study to have robust data capturing mechanisms which was only possible as it was a large industry funded investigator led RCT.

4.5.4 Meta-analysis

Meta-analysis combines the results of multiple studies to address the research question. Comparing nonrandomised with randomised studies should be taken with caution. The low deep SSI event rates and high risk of bias that exists in most of the non-randomised studies in this review have the potential to exaggerate treatment effects when compared to an adequately powered RCT (Afshari, Wetterslev, and Smith 2017; Sharma, Nazareth, and Petersen 2019).

The only two studies that may have been potentially suitable to pool together due PICO characteristics would have been the FHIT trial (Sprowson et al. 2016)and the WHiTE 8 trial (Sprowson et al. 2016; Nickil R. Agni et al. 2023). However, with only two studies available and where the WHiTE 8 trial has almost 6 times the sample size of the FHIT study there would be little benefit in this analysis with the predominant one-sided weighting of the WHiTE 8 trial. There is enough methodological heterogeneity

between the studies that has already been qualitatively discussed making them incompatible for pooling of results.

4.5.5 Ongoing trials

The DAICY trial (Mukka et al. 2022) is a RCT embedded within the Swedish arthroplasty registries replicating the intervention groups in the UK WHiTE 8 trial. It is a pragmatic cluster randomised crossover-controlled trial in hip fracture patients over the age of 60. The study will run over 4 years where centres will be allocated to one cluster and then after 2 years, they will switch to the alternate cluster for a further 2 years. It has appropriately been estimated for sample size based on its cluster randomisation methodology and is using absolute reduction in deep SSI from 3% in control group to 1.5% in intervention group for its power calculation. This is identical to the methodology used for the power calculation in WHiTE 8. It is of interest to note though that the overall event rate of infection in WHiTE 8 was 1.5%, significantly lower than the estimates used in the sample size calculation. Hence although sample size was increased by 16.5% to account for participant attrition this increased sample size would still be underpowered to detect a true difference between groups if it did exist.

The key differences between the DAICY trial and WHiTE 8 trial are that follow up period is one year in the DAICY trial compared to 90 days in WHiTE 8 and that in the DAICY trial, the definition of deep SSI is pragmatically decided by the treating physician. The DAICY trial would be the only other potentially well conducted RCT looking at the hemiarthroplasty population that would be appropriate to pool with WHiTE 8 for meta-analysis.

4.5.6 Implications for practice

UK practice for cemented hemiarthroplasties is to use ALBC as standard. Both single and dual ALBC are considered standard of care with decisions on which to use agreed locally in individual orthopaedic units. This systematic review of both randomised and non-randomised studies does not support the use of high dose dual ALBC for the reduction of deep SSI in patients receiving a hemiarthroplasty for neck of femur fractures, with the only well conducted RCT showing no difference between intervention groups (Nickil R. Agni et al. 2023).

There is an excess cost implication of the use of high dose dual ALBC and a health economic analysis of the WHiTE 8 trial has been published (Png et al. 2023). The excess was estimated to be a mean cost of £224 (95%CI -408 to 855) with almost the same QALYs 0.001 (95%CI -0.002 to 0.003). Considering there are around 32,000 hip fractures a year nationally treated with a cemented hemiarthroplasty

(Royal College of Physicians 2023) there is a considerable cost saving that can be made by not using high dose dual antibiotic cement.

Future evidence may alter the recommendations and so a re-evaluation and update of this systematic review should be carried out after the publication of the DAICY trial which is estimated to be complete in 2027.

4.5.7 Strengths and Weaknesses

This systematic review followed the methodology set out in the PROSPERO registered protocol (Ref CRD42022360341, appendix 7.3.1.) and was reported in line with PRISMA and SWiM guidelines (Page et al. 2021; Campbell et al. 2020). A key strength of this review is that there is a gap in the evidence with no published systematic review in this population and this study contributes to wider knowledge. The literature searches outlined in appendix 7.3.2 were extensive and broad and included non-English studies. Although surgical practice outside of the UK is varied and may not be applicable to the UK population it was important to keep searches broad due to the paucity of studies in the research area of question. Two Spanish studies were identified that were already published in English, but no studies were found that required translating. Odds ratios were presented or easily calculated in studies which allowed for ease of comparison across studies in the primary outcome. One study (Savage, McCormick, and Al-Dadah 2019) presented no statistical testing but did present raw data and so odds ratio could be calculated with the Haldane – Anscombe correction due to the high dose dual ALBC group having a 0% SSI rate.

The evidence in for this topic is limited but despite this I have fully considered clinical and methodological heterogeneity in the evidence available. I have explicitly considered this information to make an informed decision on the appropriateness of pooling data and presented forrest plots without pooled estimates as per SWiM guidelines (Campbell et al. 2020). I deemed the data unsuitable to pool results and meta-analyse the data and therefore in this review kept to a qualitative narrative synthesis and analysis.

One reviewer (NA) performed the quality assessment of studies and thus there could have been the introduction of error on how the NOS and RoB2 tool was applied. I was also one of the key authors of one of the studies (Nickil R. Agni et al. 2023) that I quality assessed which could have potentially been considered a weakness of methodology in this systematic review. However, the decision-making narrative for both risk of bias tools has been provided in this review and appendix for complete

transparency and reproducibility. I am therefore confident that the risk of this weakness has been mitigated.

Grey literature was not included in the searches due to time constraints and may contribute to increased publication bias (Paez 2017). A limitation of this review is that two studies (Sprowson et al. 2016; Tyas et al. 2018) were carried out on the same population in the same trust with overlapping time frames. My decision was to include both studies as although the 848 patients in the FHIT trial were likely included in the 1941 patients in the study by Tyas et al (2018), there was no way to check for non-duplicated exclusions. The two studies were also different study types with the FHIT trial having a much lower risk of bias due to its quasi-randomised methodology and more rigorous statistical analysis. Tyas et al (2018) scored as a 'poor' study on the Newcastle Ottawa Scale but was included as it had a much larger sample size compared to other included retrospective cohort studies in this review. Although double counting studies can lead to spurious high precision in the meta-analysis and cause a potential source of bias, I did not carry out a meta-analysis in this systematic review and thus risk was negated. The double counting of studies is becoming an increased problem but there is no clear guidance on how to deal with this and therefore recommendation need to be developed for future systematic reviews with planned meta-analysis (Hussein et al. 2022).

4.6 Conclusion

This systematic review of the published literature for patients receiving a cemented hemiarthroplasty after a hip fracture recommends the use of low dose single antibiotic loaded bone cement to fix their prosthesis to host bone. I have shown from this review that the use of low dose single antibiotic loaded bone cement is superior to plain bone cement, but current evidence does not support inferiority when compared to the use of high dose dual antibiotic loaded bone cement. This recommendation should be interpreted with caution due to the limited high-quality evidence in the literature.

5 Discussion

5.1 Thesis summary

RCTs underpin evidence-based health care (Hariton and Locascio 2018). However, whilst they are excellent tools for looking at a single clinical outcome, they have drawbacks in assessing secondary outcomes. One of these is the prevalence of adverse events. For common ones, usually minor, there is less of an issue as the trial typically has sufficient statistical power to assess common events if they occur more frequently than the primary outcome. It is particularly a problem where a clinically important event is rare.

Fragility fractures are a significant global burden with the projections of demand in England set to increase to around 100,000 patients annually by 2023 (Johnell and Kanis 2004; White and Griffiths 2011). Although SSIs are relatively rare as shown in the results of the WHiTE 8 trial (Nickil R. Agni et al. 2023) , strategies to reduce this complication are beneficial to both patients and to hospitals so that resources can be used elsewhere efficiently. The effectiveness of reducing SSI and safety of antibiotic loaded bone cement on renal function are issues addressed in this thesis.

Another issue affecting trials is improving their recruitment of patients. Recruitment problems affect around 50% of trials. The evidence for strategies to improve recruitment to trials is limited with a paucity of literature directed towards interventions on recruiters (Treweek et al. 2018). This thesis has addressed this issue by evaluating two strategies, targeted at trial recruiters, that aimed to improve recruitment to the WHITE 8 trial.

5.2 Key findings

There were three broad questions that were addressed in this thesis:

1. Does the use of gentamicin in systemic prophylactic antibiotics +/- in antibiotic loaded bone cement lead to increased risk of acute kidney injury post operatively in patients with hip fracture receiving a cemented hemiarthroplasty?
2.
    a. Can we improve the recruitment rate of patients to the WHiTE 8 trial by delivering a complex education intervention to trainee principal investigators?
    b. Can we improve the recruitment rate of patients to the WHiTE 8 trial by positively reinforcing recruiter behaviour after randomisation through an additional personalised email?

3. What is current evidence for the use of antibiotic loaded bone cement (ALBC) in patients with hip fracture receiving a cemented hemiarthroplasty?

This thesis presents original knowledge on the use of gentamicin in systemic and ALBC prophylaxis on the rate of AKI in hip fractures. Using two statistical analytical methods on 3178 hip fractures, I have shown that there is no unfavourable relationship between higher doses of gentamicin systemically and within ALBC on AKI rate.

Using the SWAT repository and a previous published systematic review on interventions to improve recruitment to trials (Clarke et al. 2015; Bower et al. 2014; Treweek et al. 2018), I determined that there was a gap in the literature in interventions directed to recruiters to trials. I therefore investigated the second question in the thesis aims with a 2x2 cluster factorial trial embedded into the WHiTE 8 trial. I evaluated the effectiveness of an educational intervention to TPIs and a positive reinforcement intervention via an email (digital) nudge. The conclusion of this SWAT was that a complex educational package directed to trainee principal investigators is effective at improving recruitment to a trial. There was no evidence that a digital nudge in isolation influenced recruitment but showed an additive positive effect on recruitment when combined with a complex educational intervention.

There was no systematic review of the use of ALBC in hip fractures, so my final piece of original work was to evaluate the literature completely in this topic. The conclusion of the WHiTE 8 trial was that there was insufficient evidence to support the use of high dose dual ALBC as prophylaxis in hip fractures to reduce the SSI rate. My systematic review identified six studies of which the WHiTE 8 study was overwhelmingly the largest study. The analysis showed that the literature supported the use of ALBC over plain bone cement but there is insufficient evidence to support the use of high dose dual ALBC in hip fractures to reduce risk of SSI.

The strengths and weaknesses of each study within this study has been discussed in preceding chapters.

5.3 Implications of thesis

5.3.1 Clinical trial completion

Randomised clinical trials are an essential research tool to answer research questions and recommend the future direction of clinical practice. Other than failing to recruit and retain participants in a trial there are ethical scenarios for why trials may be stopped early. These scenarios are classified as concerns based on benefit, futility and safety (Deichmann, Krousel-Wood, and Breault 2016).

Numerous trials have stopped early from perceived benefit from the intervention arm on interim analysis (Sidhu et al. 2022; "A Randomized Trial of Intensive versus Standard Blood-Pressure Control" 2015) and others due to futility i.e. intervention is unlikely to be beneficial even if continued to planned sample size (Walter et al. 2020). The scenario of safety would be considered as a reason for early closure of a trial if the participants were subject to more harm than benefit from the intervention or harm from a serious unexpected adverse incident. Examples of trials that have stopped early include a trial on preterm infants with bronchopulmonary dysplasia (Peltoniemi et al. 2005) and several HIV/AIDS trials (Mills et al. 2006).

Whilst the Data Safety and Monitoring Committee monitored the adverse events in the WHiTE 8 trial including that of AKI, I was independently able to investigate and provide reassurance with the results from my study (chapter 2) prior to most participants being recruited to the WHiTE 8 trial. Whilst I was setting sites up for WHiTE 8 nationally a common question asked by local research was with regards to AKI risk with higher doses of gentamicin in the intervention arm involving Copal G+C. My study involved an analysis of a large dataset specific to the trauma population and fills a gap in published literature on the topic. This helped to alleviate concerns and reassure research teams that giving higher doses of gentamicin in ALBC even if given alongside systemic doses does not result in a clinically detectable acute kidney injury. It also helped to contribute to equipoise across clinicians at recruitment sites concerned with this issue to maximise participant recruitment to the WHiTE 8 trial.

5.3.2 Research waste in randomised control trials

Research waste refers to studies that never contribute to the body of evidence and can be due to many reasons e.g., failure to complete, unpublished data, inadequate reporting, and avoidable design limitations (Zheutlin et al. 2020; Ioannidis et al. 2014; Correction Chalmers et al. 2014; Glasziou et al. 2014). Therefore, avoiding research waste should be key to any researcher embarking on designing and conducting a RCT. One systematic review of RCTs registered between January 2011 and December 2012 found that 85% (259 of 304 studies) showed at least one feature of waste and only 73% were

published (Chapman et al. 2019). Another study of phase 3 RCTs conducted in the United States between January 2013 and December 2014 found that 24.13% of trials were discontinued before completion with 21.11% of these due to poor recruitment (Zheutlin et al. 2020).

Clearly, failure to recruit to sample size would constitute an example of significant research waste especially in the context of large RCTs such as WHiTE 8 where significant resources are allocated for trial management and delivery. My study within a trial (SWAT) has tested two novel methods of incentivising and training site recruiters with demonstratable success on recruitment rates with regards to a complex educational intervention to trainee principal investigators (TPIs) in isolation and in conjunction with a personalised digital nudge to randomisers to the WHiTE 8 trial. No previous research has been directed towards enhancing TPi led recruitment and considering this role is now used regularly across UK orthopaedic RCTs, the beneficial findings of my SWAT can be applied to future RCT design. Whilst multicentre trials that are commercially funded are less likely to fail (Zheutlin et al. 2020), a faster recruitment timeline can also be advantageous from trial management cost savings if completed much earlier than expected.

5.3.3 Antibiotic loaded bone cement

Bone cements have been used in orthopaedic hip surgery for several decades with the focus of research being on prevention of infection in the elective total hip and knee elective population (chapter1). There was a gap in the current literature with regards to the use of ALBC for prevention of SSI in hip fractures. Through the WHiTE 8 RCT and a systematic review I have been able to add to the body of evidence in an impactful way. The current recommendation from work in this thesis is that low dose single ALBC should be used in hip fracture treatment to reduce risk of SSI with no added benefit from alternative use of high dose dual ALBC. Ongoing trials and clinical implication for practice have been discussed in Chapter 4.

5.4 Further research

There are three main areas I think where future studies may be beneficial. Firstly, further evaluation of my SWAT interventions as detailed in chapter 3.4.5 and 3.4.6. In summary the intervention should be evaluated by different trial management staff, evaluated in further RCTs and results pooled, intervention assessed for recruitment fatiguability and finally, evaluation of the cost of the intervention.

Secondly, a key limitation of the WHiTE 8 trial was the loss of power from a lower-than-expected event rate for deep surgical site infection. As outlined in my systematic review chapter, updating the review,

and performing a meta-analysis after completion of the DAICY trial will give a definitive recommendation on the use of high dose dual ALBC in hip fracture SSI prophylaxis. Thirdly, potential areas of further research using high dose dual ALBC are for high-risk elective total hip replacement (e.g., high body mass index or immunosuppression), or in aseptic revision hip surgery where the risk of SSI is higher than routine low risk elective hip surgery. However, a RCT for this would be extremely expensive and hard to justify after the results of WHiTE 8 trial showing no difference from the use of high dose dual ALBC on SSI rate. Any plans for further trials would have to wait till after publication of the DAICY trial and only justified the cost of an RCT if there was a positive effect of high dose dual ALBC on the prevention of SSI.

6 Conclusion

This thesis has undertaken three original studies alongside the WHiTE 8 trial. These studies are well designed, conducted and reported and have added unique findings to the existent evidence body in each respective area this thesis investigates. This includes original strategies to improve RCT design to aid trial recruitment via a study within a trial, evaluating the safety of ALBC on AKI risk and effectiveness of ALBC on SSI risk in hip fracture patients receiving a cemented hemiarthroplasty.

This thesis concludes that there are no safety concerns with the use of Heraeus Palacos and Copal gentamicin containing antibiotic loaded bone cement either in isolation or in conjunction with systemic investigated doses of 4.5mg/kg and 3mg/kg of gentamicin administration on rates of acute kidney injury in hip fracture patients. This informs and will reassure anti-microbial practices in hip fractures receiving a hemiarthroplasty and results are generalisable worldwide.

The published evidence appraised by systematic review for gentamicin containing high dose dual ALBC does not show reduction of deep surgical site infection in hip fractures. This not only fills a gap in the current knowledge but can be widely applied to the management of hip fractures requiring a cemented hemiarthroplasty, reducing unnecessary expenditure on a cement type without proven benefits. Further high-quality trials in progress will provide further evidence and an update of my systematic review with potential meta-analysis will definitively conclude this research question.

There are limited effective SWAT interventions that improve trial recruitment rate. This thesis concludes that enhanced trainee principal investigator packages in isolation and in conjunction with digital nudges to participant randomisers improve recruitment rates in a pragmatic orthopaedic trial. Further research of these interventions is needed to robustly conclude their effect but initial work in this field is promising and has demonstrated success in application to a large multicentre randomised clinical trial with relative ease.

7 Appendix

7.1 WHiTE 8 Appendix

7.1.1 WHiTE 8 protocol publication

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TRAUMA

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 multicentre, 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.

Cite this article: *Bone Jt Open* 2021;2-2:72–78.

Keywords: Hip fracture, Hemiarthroplasty, High dose antibiotic loaded cement, Deep infection, Randomized clinical trial

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doi: 10.1302/2633-1462.22.BJO-2020-0174

Bone Jt Open 2021;2-2:72–78.

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

Hyperlink to WHiTE 8 protocol publication

Articles

High-dose dual-antibiotic loaded cement for hip hemiarthroplasty in the UK (WHiTE 8): a randomised controlled trial

Nickil R Agni, Matthew L Costa*, Juul Achten, Nicholas Peckham, Susan J Dutton, May Ee Png, Mike R Reed, for the WHiTE 8 Investigators†*

Summary

Background Hip fracture is the most common injury requiring treatment in hospital. Controversy exists regarding the use of antibiotic loaded bone cement in hip fractures treated with hemiarthroplasty. We aimed to compare the rate of deep surgical site infection in patients receiving high-dose dual-antibiotic loaded cement versus standard care single-antibiotic loaded cement.

Methods We included people aged 60 years and older with a hip fracture attending 26 UK hospitals in this randomised superiority trial. Participants undergoing cemented hemiarthroplasty were randomly allocated in a 1:1 ratio to either a standard care single-antibiotic loaded cement or high-dose dual-antibiotic loaded cement. Participants and outcome assessors were masked to the treatment allocation. The primary outcome was deep surgical site infection at 90 days post-randomisation as defined by the US Centers for Disease Control and Prevention in an as-randomised population of consenting participants with available data at 120 days. Secondary outcomes were quality of life, mortality, antibiotic use, mobility, and residential status at day 120. The trial is registered with ISRCTN15606075.

Findings Between Aug 17, 2018, and Aug 5, 2021, 4936 participants were randomly assigned to either standard care single-antibiotic loaded cement (2453 participants) or high-dose dual-antibiotic loaded cement (2483 participants). 38 (1·7%) of 2183 participants with follow-up data in the single-antibiotic loaded cement group had a deep surgical site infection by 90 days post-randomisation, as did 27 (1·2%) of 2214 participants in the high-dose dual-antibiotic loaded cement group (adjusted odds ratio 1·43; 95% CI 0·87–2·35; p=0·16).

Interpretation In this trial, the use of high-dose dual-antibiotic loaded cement did not reduce the rate of deep surgical site deep infection among people aged 60 years or older receiving a hemiarthroplasty for intracapsular fracture of the hip.

Funding Heraeus Medical. Supported by the UK National Institute for Health and Care Research Oxford Biomedical Research Centre.

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See Online/Comment https://doi.org/10.1016/S0140-6736(23)01089-9

*Joint first authors

†The full list of WHiTE 8 Investigators is available in the appendix (pp 3–4)

Northumbria Healthcare NHS Foundation Trust, Trauma and Orthopaedics, Ashington, UK (N R Agni BSc, M R Reed MD FRCS); **Oxford Trauma and Emergency Care, Kadoorie Centre** (Prof M L Costa PhD, J Achten PhD) **and Oxford Clinical Trials Research Unit, Centre for Statistics in Medicine, Botnar Research Centre** (N Peckham MSc, S J Dutton MSc), **Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK**; **Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK** (M E Png PhD)

Correspondence to: Prof Matthew L Costa, Oxford Trauma and Emergency Care, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, Kadoorie Centre, University of Oxford, Oxford OX3 9DU, UK **matthew.costa@ndorms.ox.ac.uk**

See Online for appendix

Introduction

Hip fracture in older people (60 years and older) is a global problem that significantly impacts health-related quality of life,[1] and places a huge socioeconomic burden upon health-care systems.[2] Globally, the incidence of hip fractures is projected to reach 6·26 million per year by 2050.[3]

Approximately half of hip fractures occur at the neck of the femur, and the majority of patients older than 60 years with such an intracapsular fracture are treated with a partial hip replacement—hemiarthroplasty—in which the head of the femur is replaced with a metal implant.[4] Recent evidence suggests that the hemiarthroplasty should be fixed to the patient's bone using bone cement.[5] However, there is controversy about what type of bone cement is best.

Mortality after hip fracture surgery remains very high, with reports ranging from 10% to 40% in the first year, with much of this attributed to post-operative complications.[6–8] One of the most catastrophic of the post-operative complications is deep surgical site infection (SSI), with rates reported in the literature as high as 7·3%, and 1-year mortality rate attributed to infected hip hemiarthroplasties being up to 50%.[9–11]

High-dose dual-antibiotic loaded cement has been proposed to reduce the risk of SSI.[12–14] However, there has been some concern that widespread use of high-dose dual-antibiotic loaded cement might increase the risk of antibiotic resistant infections, and increase the chance of renal toxicity.[15,16]

The aim of the World Hip Trauma Evaluation (WHiTE) 8 randomised controlled trial was to compare the rate of deep surgical site infection in patients having hemiarthroplasty for a hip fracture receiving high-dose dual-antibiotic loaded cement versus standard care single-antibiotic loaded cement.

Hyperlink to WHiTE 8 results publication

THE BONE & JOINT JOURNAL EST. 1948

■ TRAUMA

Cost-utility analysis of dual-antibiotic cement versus single-antibiotic cement for the treatment of displaced intracapsular hip fractures in older adults

THE WHITE-8 TRIAL

M. Ee Png, M. Costa, A. Nickil, J. Achten, N. Peckham, M. R. Reed, on behalf of the WHiTE-8 Investigators

From University of Oxford, Oxford, UK

Aims

To compare the cost-effectiveness of high-dose, dual-antibiotic cement versus single-antibiotic cement for the treatment of displaced intracapsular hip fractures in older adults.

Methods

Using data from a multicentre randomized controlled trial (World Hip Trauma Evaluation 8 (WHiTE-8)) in the UK, a within-trial economic evaluation was conducted. Resource usage was measured over 120 days post randomization, and cost-effectiveness was reported in terms of incremental cost per quality-adjusted life year (QALY), gained from the UK NHS and personal social services (PSS) perspective in the base-case analysis. Methodological uncertainty was addressed using sensitivity analysis, while decision uncertainty was handled using confidence ellipses and cost-effectiveness acceptability curves.

Results

The base-case analysis showed that high-dose, dual-antibiotic cement had a significantly higher mean cost (£224 (95% confidence interval (CI) -408 to 855)) and almost the same QALYs (0.001 (95% CI -0.002 to 0.003)) relative to single-antibiotic cement from the UK NHS and PSS perspective. The probability of the high-dose, dual-antibiotic cement being cost-effective was less than 0.3 at alternative cost-effectiveness thresholds, and its net monetary benefit was negative. This finding remained robust in the sensitivity analyses.

Conclusion

This study shows that high-dose, dual-antibiotic cement is unlikely to be cost-effective compared to single-antibiotic cement for the treatment of displaced intracapsular hip fractures in older adults.

Cite this article: *Bone Joint J* 2023;105-B(10):1070–1077.

Introduction

Hip fractures impose a significant economic burden on society, with total hospital costs amounting to around £1.1 billion (2012/13 prices) annually in the UK.[1] The most common type of hip fracture, the displaced intracapsular fracture, is usually treated with a hemiarthroplasty. Among patients undergoing hemiarthroplasty, around 90% are cemented, according to the 2018 National Hip Fracture Database (NHFD).[2] The most recent evidence comparing cemented versus modern uncemented hemiarthroplasty suggests that this proportion will increase around the world.[3,4] In many healthcare systems, it is standard practice for patients having a cemented hemiarthroplasty to receive both parenteral antibiotics and antibiotic-loaded cement, due to the high risk of postoperative surgical site infection (SSI).[5] However, it is unknown if a high-dose, dual-antibiotic cement would lead to fewer infections compared with standard, single-antibiotic cement, and whether the former would be cost-effective relative to the latter.

The primary objective of the World Hip Trauma Evaluation 8 (WHiTE 8) trial was to quantify the rate of 'deep infection' within 90 days post hip fracture surgery in the single-antibiotic versus

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doi:10.1302/0301-620X.105B10.BJJ-2023-0633 $2.00

Bone Joint J 2023;105-B(10):1070–1077.

Hyperlink to WHiTE 8 health economic publication

7.1.4 Supplementary table from WHiTE 8 publication

Table S11. Breakdown of complications by allocation

	Standard care single antibiotic cement n (%)	High dose dual antibiotic cement n (%)
Participants with at least 1 complication	**953 (38.9)**	**980 (39.5)**
Chest infections/pneumonia	306 (10.2)	340 (11.3)
Urinary tract infection	296 (9.9)	313 (10.4)
Cerebrovascular accident	35 (1.2)	34 (1.1)
Myocardial infarction/acute coronary syndrome	38 (1.3)	41 (1.4)
Received blood transfusion	196 (6.6)	180 (6)
Acute kidney injury	153 (5.1)	135 (4.5)
Pulmonary embolism	11 (0.4)	16 (0.5)
Failure of fixation	3 (0.1)	6 (0.2)
Deep vein thrombosis	18 (0.6)	25 (0.8)
Additional surgery (related to hip)	47 (1.6)	49 (1.6)
Damage to a nerve, tendon or blood vessel	2 (0.1)	2 (0.1)
Dislocation	35 (1.2)	68 (2.3)
Wound infection[1]	90 (3)	54 (1.8)
Participants with SAEs	**10 (0.4)**	**5 (0.2)**

[1] *In the opinion of the treating clinician*

Hyperlink to WHiTE 8 supplementary appendix publication

7.2 Study within a trial appendix

7.2.1 EnTraP protocol publication

F1000Research F1000Research 2019, 8:1153 Last updated: 31 MAR 2022

Check for updates

STUDY PROTOCOL

Protocol for a factorial randomised controlled trial, embedded within WHiTE 8 COPAL, of an Enhanced Trainee Principal Investigator Package and Additional Digital Nudge to increase recruitment rates [version 1; peer review: 2 approved]

Nickil Agni[1,2], Caroline Fairhurst[1], Catriona McDaid[1], Mike Reed[1,2], David J. Torgerson[1]

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[2]Department of Orthopaedics, Northumbria Healthcare NHS Trust, Ashington, NE63 9JJ, UK

v1 **First published:** 22 Jul 2019, **8**:1153
https://doi.org/10.12688/f1000research.19743.1
Latest published: 22 Jul 2019, **8**:1153
https://doi.org/10.12688/f1000research.19743.1

Abstract
Recruitment remains an issue when conducting randomised controlled trials (RCTs) with a significant proportion of studies failing to reach their target sample size. Studies evaluating interventions to improve recruitment aimed specifically at recruiters to the trial are limited in number. This factorial RCT will evaluate the effectiveness of an educational intervention to trainee principal investigators and a positive reinforcement intervention via an email nudge on increasing recruitment. The targeted recruiters will be in 20 centres nationally recruiting to one large orthopaedic randomised controlled trial, WHiTE 8 COPAL. Centres will be randomised via minimisation to one of four groups. The primary outcome is recruitment rate in the first six months that a centre is actively recruiting, with data being analysed via a Poisson regression model. Results will be presented as adjusted incidence rate ratios with 95% confidence intervals. Secondary outcomes relate to the feasibility and logistics of running the interventions. We will also collect feedback regarding the educational programme set out for the trainee principal investigators. The study started in August 2018 with the anticipation of the primary objective endpoint by October 2019. The results of this study will be used to inform the design of future RCTs, particularly in orthopaedics in the UK, where the role of Trainee Principal Investigators is now a consistent one across different trials.
Trial registration: 11600053, ISRCTN, 20/08/2018; SWAT 67, Northern Ireland Hub for Trials Methodology Research SWAT repository,

Open Peer Review

Approval Status ✓ ✓

	1	2
version 1 22 Jul 2019	✓ view	✓ view

1. **Mike J. Clarke**, Queen's University Belfast, Belfast, UK

2. **Kath Star**, University of Aberdeen, Aberdeen, UK
Victoria Bell, University of Aberdeen, Aberdeen, UK

Any reports and responses or comments on the article can be found at the end of the article.

Hyperlink to EnTraP protocol publication

7.2.2 SWAT repository registration

SWAT 67: Effects of an enhanced trainee Principal Investigator package and digital nudging on monthly recruitment rates

Objective of this SWAT
The primary objective of this SWAT is to assess the effects of an enhanced trainee principal investigator (TPI) package, a digital nudge, and a combined intervention on the rate of recruitment to a randomised trial. Secondary objectives include comparing the conversion rate to recruitment from the proportion of those found to be eligible on screening across the intervention groups; gaining feedback on the trainee perspective of the TPI role via a survey; determining the time needed to conduct the 1:1 educational training session for TPIs; and determining the required time and method of additional contact for peer support of the TPIs. We will also determine the feasibility of delivering both interventions in the setting of a large-scale randomised trial.

Study area: Recruitment
Sample type: Healthcare professionals
Estimated funding level needed: Low

Background
Recruitment remains one of the major challenges for randomised trials and researchers have tried many different ways to overcome the problems of slow recruitment [1]. This SWAT will test two different approaches in a factorial, cluster randomised design: introducing an enhanced trainee principal investigator's package and email digital nudges to healthcare professionals involved in the trial. The SWAT will be implemented in the WHiTE 8 COPAL trial, which is a large multicentre trial in orthopaedics starting in 2018 (www.octru.ox.ac.uk/trials/trials-in-set-up/WHiTE-8-COPAL). The interventions have both been used in current orthopaedic trials, but their effects on recruitment have not been investigated.

Interventions and comparators
Intervention 1: Deliver an enhanced TPI package (induction & training, trial education, peer support)
Intervention 2: Use of a personalised, timely email nudge to express gratitude and encourage further recruitment to each successful healthcare recruiter
Intervention 3: Deliver an enhanced TPI intervention (induction, trial education, peer support) and use of a personalised, timely email nudge to express gratitude and encourage further recruitment to each successful healthcare recruiter
Intervention 4: Usual practice without TPI education package or nudge (comparator)

Index Type: Recruitment, Monitoring

Method for allocating to intervention or comparator
Randomisation

Outcome measures
Primary: Total number of patients recruited in 6 months to the WHiTE 8 COPAL trial.
Secondary: Conversion rate from screened population, collected monthly from the central Oxford database (coordinated by the Oxford Clinical Trials Research Unit, OCTRU).
The trainee perspective of their role will be collected through the TPI survey in the last 2 weeks of the SWAT period. The research fellow will keep a time log for delivering the TPI education intervention and a log of communication for peer support during the period of the SWAT

Analysis plans
Analysis will be conducted on an intention to treat basis including all sites in the group they were originally allocated to regardless of deviations based on non-compliance. Statistical significance will be assessed using two-sided statistical tests at the 5% significance level. Baseline data relating to the sites (including the minimisation factors) will be summarised for the four groups, as randomised and as analysed to assess whether possible loss-to-follow-up has introduced selection bias. Continuous data will be presented using descriptive statistics (e.g., mean, standard deviation, median, minimum, maximum), while categorical data will be given as counts and percentages. No formal statistical comparison of baseline data will be undertaken between the four groups.

The number of participants recruited per site will be summarised. A Poisson regression model, containing the two interventions (Enhanced TPI and Digital Nudge) and the minimisation factors (cluster size, and number recruited per month will be included in their continuous form) will be performed. Adjusted incidence rate ratios (IRRs) and associated 95% confidence intervals (CIs) will be obtained from this model. The presence of an interaction between the two interventions will also be tested by including an interaction term in the model.

Feasibility outcomes, such as the time required to run the education intervention and communication time and methods used for the peer support aspect of the intervention, will be reported descriptively.

Possible problems in implementing this SWAT
The fixed number of clusters in the host trial (WHiTE 8 COPAL) is too small to provide sufficient power for this SWAT in that trial alone. However, this first implementation will show if it is feasible to run these interventions in factorial trial and if they could be included as part of a much larger cluster study.

References
1. Treweek S, Pitkethly M, Cook J, et al. Strategies to improve recruitment to randomised trials. Cochrane Database of Systematic Reviews 2018; (2): MR000013.

Publications or presentations of this SWAT design

Examples of the implementation of this SWAT

People to show as the source of this idea: Nickil Agni, Catriona McDaid, David Torgerson, Mike Reed
Contact email address: nickil.agni@googlemail.com
Date of idea: 1/OCT/2017
Revisions made by: Nickil Agni
Date of revisions: 19/AUG/2018

Hyperlink to SWAT repository publication

7.2.3 EnTraP trial publication

Original Research Article

RESEARCH METHODS in MEDICINE & HEALTH SCIENCES

Research Methods in Medicine & Health Sciences
2022, Vol. 3(2) 33–41

DOI: 10.1177/26320843211061297
journals.sagepub.com/home/rmm
SAGE

EnTraP: A factorial randomised controlled trial embedded within world hip trauma evaluation eight COPAL investigating the effect of an enhanced trainee principal investigator package and digital nudge on recruitment rates

NR Agni[1,2], C Fairhurst[2], C McDaid[2], MR Reed[1] and DJ Torgerson[2]

Abstract

Background: Randomised controlled trials (RCTs) often struggle with various aspects of participant recruitment, including engaging clinicians to recruit effectively, and subsequently fail to reach their target sample size. Studies evaluating interventions to improve recruitment aimed specifically at recruiters to the trial are limited in number. The RCTs embedded into the World Hip Trauma Evaluation (WHiTE) cohort study use Trainee Principal Investigators (TPIs) to help manage and drive recruitment at trial sites. No formalised training or support is provided by central trials units to the TPIs. Additionally, trial recruiters receive a generic automated email confirming randomisation to the trial with no other communication to influence or incentivise their behaviour to further recruit. The primary aim of this factorial trial was to evaluate the effectiveness of an educational intervention to TPIs and a positive reinforcement intervention via an email (digital) nudge on increasing recruitment. Secondary aims included feasibility of implementing the interventions and surveying TPIs on the educational package quality of content, delivery and ongoing support.

Design: This was a multicentre, open, cluster, 2x2 factorial RCT embedded in the WHiTE 8 COPAL RCT, in which research sites were randomised 1:1:1:1 to receive the enhanced TPI package, the digital nudge intervention, both, or neither.

Results: 1215 patients were recruited to the WHiTE 8 COPAL trial across 20 sites during the SWAT between August 2018 and March 2019. There was a statistically significant interaction between the interventions (IRR 2.09, 95% CI 1.64 to 2.68, $p < 0.001$). There was a statistically significant benefit on recruitment (IRR 1.23 95% 1.09 to 1.40, $p=0.001$) from utilizing an enhanced TPI education intervention. The digital nudge intervention had no significant impact on recruitment (IRR 0.89 95% CI 0.79 to 1.01, $p=0.07$). Within enhanced TPI package sites, the digital nudge had a beneficial effect, while in the standard practice TPI sites it had a detrimental effect. Feasibility analysis showed the median time to site digital nudge and enhanced TPI set up were one day and 17 days, respectively. 353 digital nudges were created taking an average of 12 min to construct, log the activity and then disseminate to recruiters. Median induction time for enhanced TPI was 32 min and 100% of the groups were extremely satisfied with the induction content, delivery and ongoing support.

Discussion: An education and support programme targeted at surgical TPIs involving a digital education package, 1:1 telephone induction and subsequent support package was effective in increasing recruitment in the first 6 months of trial commencement. There was no evidence for the effectiveness of the digital nudge intervention in isolation, although our results show that when combined with an education programme, it leads to enhanced effectiveness of that programme.

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[2]York Trials Unit, Department of Health Sciences, University of York, York, UK

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Email: Nickil.Agni@nhs.net

Hyperlink to EnTraP trial publication

7.2.4 Ethics Confirmation

7.2.4.1 University of York

DEPARTMENT OF HEALTH SCIENCES

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Dr Stephen Holland
Chair, Health Sciences Research Governance Committee

www.york.ac.uk/healthsciences

16 March 2018

Mr N Agni
Department of Health Sciences
University of York
York
YO10 5DD

Dear Nickil

Trainee principal investigator survey
Factorial SWAT – Increasing recruitment in the WHiTE 8 Copal trial

Thank you for submitting the above projects to the Health Sciences Research Governance Committee for review. Your applications were considered by the committee at its meeting on 12 March 2018.

I am pleased to report that the committee approved the projects.

I was asked to feedback that the information sheets for both studies need version numbers/date.

If you have any queries regarding the decision or feedback, or make any substantial amendments to the study, please contact me. Finally, if you intend to submit this letter or any other correspondence from the HSRGC as part of your assessed work (e.g., to demonstrate that your study has ethical approval) please make sure you edit the letter so as to maintain anonymity.

Yours sincerely

S. Holland

Stephen Holland
Chair: HSRGC

cc: Dr Catriona McDaid, Prof David Torgerson

1

7.2.4.2 NHS REC amendment for WHiTE 8 trial

Partner Organisations:
Health Research Authority, England
NIHR Clinical Research Network, England
NHS Research Scotland
NISCHR Permissions Co-ordinating Unit, Wales
HSC Research & Development, Public Health Agency, Northern Ireland

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	WHITE 8 - COPAL *A Randomised Controlled Trial of low dose single antibiotic loaded cement versus high dose dual antibiotic loaded cement in patients receiving a hip hemiarthroplasty after fracture.*
IRAS Project ID:	233884
Sponsor Amendment Notification number:	AM06
Sponsor Amendment Notification date:	04Sep2019
Details of Chief Investigator:	
Name [first name and surname]	Professor Mike Reed
Address:	Northumbria Specialist Emergency Care Hospital Northumbria Way Cramlington, Northumberland
Postcode:	NE23 6NZ
Contact telephone number:	01670 529191
Email address:	White8-copal@ndorms.ox.ac.uk
Details of Lead Sponsor:	

Name:	Peta Heslop Clinical Trials Office, Education Centre North Tyneside General Hospital Rake Lane, North Shields Tyne & Wear, NE29 8NH Tel: 0191 2934087 Ext 34087
Contact email address:	ResearchAndDevelopment@northumbria-healthcare.nhs.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	Yes
Name of lead R&D office:	Northumbria Healthcare NHS Foundation Trust

2. Summary of amendment(s)

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

No.	Brief description of amendment *(please enter each separate amendment in a new row)*	Amendment applies to *(delete/ list as appropriate)*		List relevant supporting document(s), including version numbers *(please ensure all referenced supporting documents are submitted with this form)*		R&D category of amendment *(category A, B, C) For office use only*
		Nation	**Sites**	**Document**	**Version**	
1	Embedded study within a trial - A Factorial Randomised Controlled Trial embedded within WHiTE 8 COPAL looking at the effect of an **En**hanced **Tra**inee **P**rincipal Investigator Package and Additional Digital Nudge on recruitment rates.	England	All sites recruiting to WHiTE 8 COPAL study	Swat protocol Higher education ethical approval TPi participation information leaflet TPi induction presentation TPi induction agenda TPi follow up survey	V2.0 08Aug2019 16Mar2018 V3.0 01Apr2018 V1.0 01Aug2018 V1.0 08Jun2018 V1.0 08Feb2019	
2						
3						
4						
5						

[Add further rows as required]

3. Declaration(s)

Declaration by Chief Investigator

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment(s) to be implemented.

Signature of Chief Investigator: 

Print name: Mike Reed

Date: 21.10.20

Optional Declaration by the Sponsor's Representative (as per Sponsor Guidelines)

The sponsor of an approved study is responsible for all amendments made during its conduct.

The person authorising the declaration should be authorised to do so. There is no requirement for a particular level of seniority; the sponsor's rules on delegated authority should be adhered to.

- I confirm the sponsor's support for the amendment(s) in this notification.

Signature of sponsor's representative: .....

Print name: .....

Post: .....

Organisation: .....

Date: .....

7.2.5 Trainee survey protocol

A nationwide survey of the experiences of orthopaedic trainees in carrying out the role of a Trainee Principal Investigator in a Randomised Control Trial

INTRODUCTION AND BACKGROUND

Randomised control trials (RCTs) are considered the gold standard when evaluating the efficacy and effectiveness of health care interventions. Unfortunately, a significant number of well-designed RCTs struggle with the recruitment of clinicians and patients subsequently failing to reach target sample size.

The challenge in recruitment to RCTs has been well documented in the literature. (Puffer, Torgerson, and Watson 2003; McDonald et al. 2006; Sully, Julious, and Nicholl 2013) In the UK, 55% of NIHR trials between 2002 and 2008 met recruitment targets with 45% of all trials needing funding extensions.(Treweek et al. 2015) Many trials have also closed prematurely due to recruitment problems.(McDonald et al. 2006; Foy et al. 2003; Bower, Wilson, and Mathers 2007) A recent survey of Clinical Trials Units (CTU) in the United Kingdom found that recruitment remained their priority.(Tudur Smith et al. 2014)

The World Hip Trauma Evaluation (WHiTE) comprehensive cohort is an orthopaedic observational study collecting data on fracture neck of femurs. Within this cohort there have been many successful RCTs embedded with the next RCT, WHiTE 8 COPAL, due to start in May 2018. This trial aims to determine the rate of deep infection in patients treated with either single dose antibiotic loaded cement or high dose dual antibiotic loaded cement for the treatment of hip fracture with a hemiarthroplasty.

A recruitment strategy employed by WHiTE trials is the use of Trainee Principal Investigators. Trainee Principal investigators (TPi) are training orthopaedic registrars whose role is to work alongside local consultant principal investigators in a research study. The principal aim of the role is to co-ordinate and engage local trainees in recruiting patients to the trial especially out of normal working hours. Several multicentre orthopaedic trials have utilised trainee principal investigators at recruitment centres with anecdotal success, however the effects on recruitment rates have not been formally evaluated or published.

Within the WHiTE framework the TPi is recruited and managed locally by the consultant principal investigator. There is a trainee principal investigator manual provided from the Oxford clinical trials unit (CTU) with no further education or involvement centrally from the CTU. A study within a trial (SWAT) involving TPIs is planned to be embedded in the WHiTE 8 COPAL trial. The aim is to determine the effect on patient recruitment to the trial by introducing a package of enhanced education

and peer support to the TPis. In order to create this enhanced TPi role we must first determine the experiences and challenges currently faced by orthopaedic trainees who have been involved in orthopaedic trials as a TPi.

AIM

A survey to all orthopaedic trainees nationally.

The aim is to evaluate the experience and challenges associated with conducting the TPi role to guide the creation of an enhanced Trainee Principal Investigator intervention. A SWAT will be embedded into the White COPAL multicentre RCT to evaluate the effects of the intervention on recruitment rate.

METHODOLOGY

DESIGN

An electronic survey will be emailed to current orthopaedic trainees with a national training number. Nationally, orthopaedic trainees are organised into post graduate deaneries who are responsible for medical education and training. Each deanery has a speciality programme coordinator representing orthopaedics who will be contacted to disseminate the survey to trainees in their region.

The main areas the survey will cover include:

- General question regarding experience as a trainee principal investigator in orthopaedic trials
- Methods of recruitment and training undergone to carry out the role
- The trainees personal experience regarding if they felt valued as a recruiter
- Challenges and logistical problems related to undertaking a TPi role.
- Willingness to participate again as a TPi

PARTICIPANTS

Each deanery has a speciality programme coordinator representing orthopaedics who will be contacted to determine the number of potential trainees and their permission to disseminate a survey in their region. Where there is no response from the speciality coordinator, the British Orthopaedic Trainees Association (BOTA) representative for each region will be contacted for dissemination of the survey. The contact details for these representatives are in the public domain. No power has been attributed to the survey as we are surveying a complete sample with a fixed number of participants.

No expenses or monetary incentive will be given for participation in this survey. A certificate of completion can be provided to show engagement with research for portfolio and revalidation purposes for the trainee. This will be offered as an option at the end of the survey and will be entirely optional.

INCLUSIONS AND EXCLUSIONS

All Orthopaedic trainees will be included. These will mostly be trainees at a Specialist Registrar level but may include those out of programme, core trainees and those in LAT posts.
All other specialities will be excluded.

SURVEY

The survey will be distributed through email by the speciality programme coordinator or BOTA representative in each region. The trainee will be able to access the survey by clicking on a weblink in the email which will take them directly to the survey. No trainee will be emailed directly by the PhD student running this study. An information sheet will be provided in the email with a contact number and email address for the PhD student running the study. The information sheet will detail how the data will be used and distributed and that the individual will not be identified, and anonymity will be protected.

The first page of the survey will be a summary information sheet with a consent check box at the bottom. This box will need to be ticked and agreed with before able to start answering the survey questions.

The survey was created and will be disseminated using the website 'Qualtrics'; which also enables paper versions of the survey to be printed if participants wish they may submit these in paper form to a postal address given in the email.

ANALYSIS

The study will be reported through descriptive statistics. No adjustment will be made for incomplete data; however, response rates and summary statistics will be reported. The report will follow the Checklist for Reporting Results of Internet E-Surveys (CHERRIES)(Eysenbach 2004)

CONFLICTS

There are no conflicts of interest declared. We do not expect any ethical and legal issues arising from this survey

BURDEN

Burden will be kept to a minimum as the survey will be delivered and completed electronically. The time for completion is unlikely to be problematic as the survey will take no more than 2-10 minutes to fill out. Reminder emails will be sent at 2 weeks but nothing further following this. Consent will be obtained through the ‘Qualtrics’ survey system.

CONFIDENTIALITY

There will be no personal information collected through the survey except email addresses, which can be voluntarily provided by participants for the purpose of dissemination of results or certification of participation if requested through the survey. Email addresses will not be linked to any survey responses.

ETHICS APPROVAL

The protocol and all study documents have been approved by the University of York, Health Sciences Research Governance Committee. Approval ID: **HSRGC/2018/266/C**

INDEMNITY

The University of York Insurance office will be informed of the study. As this study is being conducted within the UK and is limited to questionnaires with Health Professionals, it is covered by the Universities 'Public Liability' insurance.

STUDY DOCUMENTS

All storage and archiving will be conducted in line with the York Trials Unit Standard Operating Procedure. All study data will be stored on a secure server accessed via a password protected computer at the University of York.

No data will be transferred as all information will be directly imported through the Qualtrics software on to the secure network at York Trials Unit.

DISSEMINATION

A summary report of the study will be distributed to trainees who took part if requested at the end of the survey by email from the PhD student. This piece of work will inform modification to an enhanced TPi intervention which will be used in the WHiTE 8 COPAL RCT. The survey may be published and referenced in any future publication related to the enhanced TPi package. The work may also by referenced in presentations to the wider orthopaedic community regarding recruitment strategies in then WHiTE 8 COPAL trial. The knowledge acquired will also form a chapter of a PhD thesis.

7.2.6 Trainee national survey participant information

UNIVERSITY of York
The Department of Health Sciences

A survey of orthopaedic trainees on becoming a Trainee Principal Investigator in a randomised control trial.

Participant Information Sheet

We would like to invite you to take part in the above-named survey but before you decide, please review the following information.

What is the purpose of this study?
Trainee Principal investigators (TPi) are training orthopaedic registrars whose role is to work alongside local consultant principal investigators in a research study. The principal aim of the role is to coordinate and engage local trainees in recruiting patients to the trial especially out of normal working hours. Several multicentre orthopaedic trials have utilised trainee principal investigators at recruitment centres with anecdotal success, however the effects on recruitment rates have not been formally evaluated or published.

The survey will evaluate the current experience of orthopaedic trainees regarding this role with the aim of improving the recruitment, education, management, and oversight of trainees involved as TPis in future RCTs.

Who is doing the study?
The survey is being run by Mr Nickil Agni who is an Orthopaedic Surgeon in Training based at the University of York Trials Unit. The York Trials Unit is sponsored by the British Orthopaedic Association to develop and expand the portfolio of trials in the UK related to trauma and orthopaedics. This work is being completed as part of an PhD project.

Who is being asked to participate?
All orthopaedic trainees who may have had experience with orthopaedic randomised control trials.

Do I have to take part?
The survey is entirely optional, and your consent will be sought at the beginning of the survey

What will be involved if I take part in this study?
The survey will be completed online. They completion time will take between 2-10mins dependent on how much involvement you have had as a TPi in a clinical trial.

What are the advantages/benefits and disadvantages/risks of taking part?
The answers provided will help identify the number of trainees involved in clinical research as TPis and current problems in recruiting to and carrying out duties within the role. This will provide us with information to better modify the TPi role in future RCTs.
There will also be certification issued if requested at the end of the survey which can be used as evidence of research participation for professional development and revalidation purposes.

Can I withdraw from the study at any time?

You can withdraw at any point up until the questionnaire is submitted. It is regrettable, but data cannot be withdrawn following questionnaire submission as all the data is anonymised and we will not be able to identify the data to withdraw.

Will the information obtained in the study be confidential? *or* Will the information I give be kept confidential?

All storage and archiving will be conducted in line with the York Trials Unit Standard Operating Procedure. All study data will be stored on a secure server accessed via a password protected computer at the University of York. No identifiable data will be collected, and email addresses will not be linked to the data. We will only collect your email address if you submit it within the form and only to provide you with a report of the findings or for issuing certification of participation.

What will happen to the results of the study?

A summary report of the study will be available. If you would like a copy, then please enter your email within the survey and a copy of the findings will be sent to you. The email address will not be linked to any information you provide within the survey.

Who has reviewed this study?

The research has been approved by the Department of Health Sciences' Research Governance Committee at the University of York. Ethics Approval ID: **HSRGC/2018/266/C**

Who do I contact in the event of a complaint?

If you have any concerns please contact Dr Catriona McDaid (Reader in Trials and Research Supervisor)
Tel: +44 (0)1904 321371 Email: catriona.mcdaid@york.ac.uk

If you agree to take part, would like more information, or have any questions or concerns about the study please contact

Mr Nickil Agni MBBS, BSc, MRCS, Orthopaedic Registrar in Training Northern Deanery, Research Fellow WHiTE 8 Copal trial.

ARRC Building, York Trials Unit, Department of Health Sciences, University of York, Heslington, YO10 5DD. Nra513@york.ac.uk. Tel: +44 (0)1904 321371

Thank you for taking the time to read this information

7.2.7 Trainee national survey

A nationwide survey of the experiences of orthopaedic trainees in carrying out the role of a Trainee Principal Investigator in a Randomised Control Trial

Dear Participant,

We would like to invite you to take part in a survey where you will be asked questions regarding any involvement you may have had as a Trainee Principal Investigator in any orthopaedic Randomised Control Trials. The answers you provide will help us to improve the trainee experience for future Randomised Control Trials.

We would be grateful if you could take 2-10min of your time to complete this survey regarding your experiences. Please complete the survey even if you have had no experience with the Trainee Principal Investigator role as it was help us to gage the level of current trainee involvement. A certificate of completion can be provided to show engagement with research for portfolio and revalidation purposes.

This survey is part of a larger piece of work involving researchers at the British Orthopaedic Association's Orthopaedic Research Centre embedded within York Trials Unit, University of York. Please contact nra513@york.ac.uk if you have any queries.

A participant information sheet can be accessed by clicking this link (link to information sheet)

Link to survey

If you would like to print this survey and return it by post, please send it to the following address:
Mr Nickil Agni, ARRC Building Ground Floor, York Trials Unit, Department of Health Sciences, University of York, Heslington, YO10 5DD

CONSENT

This question confirms your consent to participate in the study.

The decision to complete this survey is completely voluntary. If you do complete the survey, information you provide will be included in our analysis along with anonymised direct quotes.

- I confirm I have read an understood the information provided above and participation leaflet
- I understand that the completion of this questionnaire is voluntary
- I agree to the use of anonymised quotes in publications
- I agree that my data gathered in this study will be kept and stored confidentially

Do you agree with all of these statements and agree to take part in this study?
Yes
No

SURVEY

1. **At what stage of training are you currently at?**

   ST3 ST6
   ST4 ST7
   ST5 ST8

2. **Are you aware of the Trainee Principal Investigator role utilised by some orthopaedic Randomised Control trials?**

   Yes
   No – Skip to question 4

3. **Are you currently or in the past been a Trainee Principal Investigator for an RCT?**
   Yes – Skip next question 6
   No – Skip to question 5

4. **If you are not familiar with the role, would you like more information and consider getting involved with orthopaedic research as a Trainee Principal Investigator?**

   Yes – Skip to end
   No – Skip to end

5. **If you have not had the opportunity to be a Trainee Principal Investigator, would you consider the role in the future?**

   Yes – Skip to end

   No – Skip to end

6. **How were you recruited to the role?**

   (Free text box)

7. **What education or training did you receive for you to carry out your role as a Trainee Principal Investigator?**

   (Free text box)

8. **Are there any improvement to this process that you would have found useful?**

   (Free text box)

9. **Do you think your participation made a difference to patient recruitment?**

   Yes

   No

10. **Were there any challenges or limitations for you to carry out your duties as a Trainee Principal Investigator**?

    (Free text box)

11. **Would you be a Trainee Principal Investigator for a Randomised Control Trial again?**

    Yes

    No

12. **Has your experience given you the confidence to become a Consultant Principal Investigator in the future for an orthopaedic RCT?**

    Yes

    NO

    END: Thank you for taking the time to complete this survey

    Would you like a summary report of the survey sent to you via email?

    Yes – Enter email address

    NO

Would you like a certificate for your records?

Yes – Enter email address

No

7.2.8 EnTraP Trainee Pi follow up survey

TPi Follow up Survey

Start of Block: Informed Consent

A survey of the experiences of orthopaedic trainees in carrying out the role of a Trainee Principal Investigator in the WHITE 8 COPAL trial.

We would like to invite you to take part in a survey where you will be asked questions regarding any involvement you may have had as a Trainee Principal Investigator in the WHITE 8 COPAL trial.

The answers you provide will help us to improve the trainee experience for future Randomised Control Trials. Please be assured that your responses will be kept completely confidential

The study should take you around 10 to complete. If you would like to contact the Principal Investigator in the study to discuss this research, please email nra513@york.ac.uk. This question confirms your consent to participate in the study. The decision to complete this survey is completely voluntary. If you do complete the survey, the information you provide will be included in our analysis along with anonymised direct quotes.

I confirm I understood the information provided above and participation leaflet
I understand that the completion of this questionnaire is voluntary
I agree to the use of anonymised quotes in publications
I agree that my data gathered in this study will be kept and stored confidentially

- ○ I consent, begin the study
- ○ I do not consent, I do not wish to participate

Q1 What stage of training are you at?

- ○ ST3
- ○ ST4
- ○ ST5
- ○ ST6
- ○ ST7
- ○ ST8
- ○ Other _____

Q2 Have you been a Trainee Principal Investigator (Associate Pi) in the past?

- ○ Yes
- ○ No

Q3 How were you recruited to become a White 8 TPi?

_____

Q4 Did you receive a telephone induction by the White 8 research fellow?

- ○ Yes
- ○ No
- ○ Unable to remember

Skip To: Q6 If Did you receive a telephone induction by the White 8 research fellow? = No

Q5 The following Questions will explore your experience regarding the telephone induction you received from the White 8 Fellow

Q5a Did you receive enough time to review the digital package emailed in advance to your induction?

- ○ Yes
- ○ Yes, but I would have preferred more time
- ○ Unsure
- ○ No
- ○ I did not receive the documents

Q5b Did you feel any information relevant to the induction was missing in the digital package?

- ○ No
- ○ Yes _____

Q5c How useful was the induction at clarifying the purpose of the trial?

- ○ Extremely useful
- ○ Very useful
- ○ Moderately useful
- ○ Slightly useful
- ○ Not at all useful

Q5d How useful was the induction at clarifying the consenting and randomisation process in White 8?

- ○ Extremely useful
- ○ Very useful
- ○ Moderately useful
- ○ Slightly useful
- ○ Not at all useful

Q5e How useful was the induction at clarifying your role as a TPi?

- ○ Extremely useful
- ○ Very useful
- ○ Moderately useful
- ○ Slightly useful
- ○ Not at all useful

Q5f How useful was the induction at clarifying the benefits of being a TPi?

- ○ Extremely useful
- ○ Very useful
- ○ Moderately useful
- ○ Slightly useful
- ○ Not at all useful

Q5g Did the Induction allow enough time for your questions?

- ○ Yes
- ○ No

Q5h How satisfied were you with the induction process?

- ○ Extremely satisfied
- ○ Somewhat satisfied
- ○ Neither satisfied nor dissatisfied
- ○ Somewhat dissatisfied
- ○ Extremely dissatisfied

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q6 The following questions will explore your experience with regards to preparation for your role as Trainee Principal Investigator

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q6a Did you receive an induction? Please elaborate regarding what the induction involved if you answer "yes"

- ○ No
- ○ Yes _____

Skip To: Q6c If Did you receive an induction to the role locally? Please elaborate regarding what the induction i... = No

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q6b How useful was the induction provided to you clarify the purpose of the trial?

- ○ Extremely useful
- ○ Very useful
- ○ Moderately useful
- ○ Slightly useful
- ○ Not at all useful

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? != Yes

Q6c Was it clear to you what your role entailed?

- ○ Extremely clear
- ○ Somewhat clear
- ○ Neither clear nor unclear
- ○ Somewhat unclear
- ○ Extremely unclear

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? != Yes

Q6d Was it clear to you the benefits of being a TPi?

- ○ Extremely clear
- ○ Somewhat clear
- ○ Neither clear nor unclear
- ○ Somewhat unclear
- ○ Extremely unclear

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? != Yes

Q6e How confident were you with the consenting and randomisation process?

- ○ Extremely confident
- ○ Very confident
- ○ Moderately confident
- ○ Slightly confident
- ○ Not confident at all

Display This Question:

If Did you receive an induction to the role locally? Please elaborate regarding what the induction i... = Yes

And Did you receive a telephone induction by the White 8 research fellow? != Yes

Q6f How satisfied were you with any local induction process you had?

- ○ Extremely satisfied
- ○ Somewhat satisfied
- ○ Neither satisfied nor dissatisfied
- ○ Somewhat dissatisfied
- ○ Extremely dissatisfied

Q7 Do you have any suggestions about how training and support for the TPI role could be improved? Please elaborate if you answer "yes"

- ○ No
- ○ Yes _____

Q8 Were there any challenges with being a TPi at your centre that made it difficult for you to carry out your role?

- ○ No
- ○ Yes _____

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q9 The following questions will explore your experience with regards to communication with the White 8 Research fellow

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q9a How supported in your role were you by the White 8 Research Fellow?

- ○ Extremely supported
- ○ Somewhat supported
- ○ Neither supported nor unsupported
- ○ Somewhat unsupported
- ○ Extremely unsupported

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q9b How useful was the periodic contact to identify and resolve issues?

- ○ Extremely useful
- ○ Very useful
- ○ Moderately useful
- ○ Slightly useful
- ○ Not at all useful

Display This Question:

If Did you receive a telephone induction by the White 8 research fellow? = Yes

Q9c How satisfied were you with the frequency of contact by the White 8 research fellow?

- Extremely satisfied
- Somewhat satisfied
- Neither satisfied nor dissatisfied
- Somewhat dissatisfied
- Extremely dissatisfied

Q10 How supported in your role were you by your consultant Pi?

- Extremely supported
- Somewhat supported
- Neither supported nor unsupported
- Somewhat unsupported
- Extremely unsupported

Q11 How likely would you consider becoming a TPi again for another trial?

- Extremely likely
- Somewhat likely
- Neither likely nor unlikely
- Somewhat unlikely
- Extremely unlikely

Q12 Do you feel that your participation made a difference to recruitment at your centre?

- ○ Definitely yes
- ○ Probably yes
- ○ Might or might not
- ○ Probably not
- ○ Definitely not

Q13 How likely are you to consider becoming a consultant Principal investigator in the future?

- ○ Extremely likely
- ○ Somewhat likely
- ○ Neither likely nor unlikely
- ○ Somewhat unlikely
- ○ Extremely unlikely

End of Block: Informed Consent

7.2.9 EnTraP TPi Induction documentation

7.2.9.1 Induction agenda

UNIVERSITY of York
The Department of Health Sciences

WHiTE 8 COPAL Randomised Control Trial

Trainee Principal investigator Induction Agenda

Thank you for participating in this study. This agenda will form the basis of your induction session with the WHiTE 8 Copal Research fellow. During your induction session you will need to have access to a computer to review key documents. The session will take approximately 40mins.

AGENDA

	TOPIC	Time Allotted
1	Introduction + Background to the trials	5 mins
2	The Trainee Principal Investigator Role • Towards Patients • Toward Trainees • Towards Research team	5 mins
3	Benefits to the TPi	2 mins
4	How to recruit and randomise a patient to the WHiTE 8 COPAL trial?	10 mins
5	Suggestions regarding how to perform your role	10 mins
6	TPi Contact information for support	2 mins
7	Supplementary documents review	5 mins

If you agree to take part, would like more information or have any questions or concerns about the study please contact

Mr Nickil Agni MBBS, BSc, MRCS, Orthopaedic Registrar in Training Northern Deanery, Research Fellow WHiTE 8 Copal trial.

ARRC Building York Trials Unit, Department of Health Sciences, University of York, Heslington, YO10 5DD. Nra513@york.ac.uk. Tel: +44 (0)1904 321371

Thank you for taking the time to read this information

Version 1.1
08/07/2018
Ethics Approval ID: **HSRGC/2018/266/C**

7.2.9.2 Oxford TPi manual

Trainee Principal Investigator Manual

Version: 1.0

Authors: Damian Haywood (Operational Lead), Miguel Fernandez (StR Orthopaedics & Trauma)

Contact: 01865 223114

Twitter: @Oxford_Trauma

1 Introduction

This manual has been put together to provide information on the benefits, roles and responsibilities of becoming a trainee Principal Investigator (tPI) with Oxford Trauma. With the aim of providing tPI all the information required to understand the role of Principal Investigators in clinical trials; recruit and retain patients in Oxford Trauma trials; and understand what standards Oxford Trauma as part of a registered trials unit (Oxford Clinical Trials Research Unit, www.octru.ox.ac.uk) expect of participating PIs and tPIs.

2 A brief overview of Oxford Trauma

The Oxford Trauma research group within the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, is led by Professor Matt Costa. The group is passionate about improving healthcare in musculoskeletal trauma, using excellent research and clinical trials in orthopaedic trauma with the primary aim to inform National Institute for Health and Care Excellence (NICE) guidelines.

Our team is based at the Kadoorie Critical Care Research Centre located at the John Radcliffe Hospital, Oxford. We work closely with OCTRU (the NDORMS clinical trials unit) and RRIO (our rehabilitation sibling) in delivery of high quality, cost effective, and patient-centred clinical trials. Our current studies include, WHiTE Four (https://white4.octru.ox.ac.uk/), WHiTE Five (https://white5.octru.ox.ac.uk/), WHiTE 7-WHISH, WHIST (https://whist.octru.ox.ac.uk/), UK STAR (https://ukstar.octru.ox.ac.uk/), TrAFFix (https://traffix.octru.ox.ac.uk/), and DRAFFT2 (https://drafft2.octru.ox.ac.uk/).

Further information can be found on our website: https://www.ndorms.ox.ac.uk/research/Oxford-Trauma.

3 Background

A significant factor in the successful recruitment and retention of patients in research is the structure and relationships within clinical research teams, in particular the low tacit status of recruitment skills. Explaining a clinical trial to patients is a task best performed by a treating clinician, most notably the PI, since the patient's trust is with the clinician, they must be an active player when enrolling patients. It is also our belief and aim that each eligible patient should be considered by the clinician as a potential trial candidate. By having dedicated tPIs and providing this

training package we believe this will improve the patient experience of taking part in research, and improve recruitment and retention into trials.

4 Principal Investigator

A fundamental aspect of your role as tPI is to understand the role and responsibilities of a trial PI. You will not be required to undertake these responsibilities fully, but they are listed here as an indication. International conference of Harmonisation GCP (ICH GCP) guidelines[i], define an investigator as "A person responsible for the conduct of the clinical trial at a trial site." As a tPI you will be supporting the PI to achieve the following tasks and responsibilities. PIs are responsible for ensuring:

- The dignity, rights, safety and wellbeing of participants are given priority at all times
- The study follows the approved protocol
- Procedures are in place to ensure the collection, processing and storage of high quality accurate data in accordance with the Data Protection Act 1998 and the Caldicott Principles
- Each member of the research team, is suitably qualified by education, training and experience to conduct the study, and their qualifications and training details are documented
- The study is conducted by the PI personally and/or members of your research team through authorised delegated responsibility
- All necessary employment contracts, including honorary research contracts/letters of access, and other access arrangements are in place before the study starts
- Students, new researchers and those with delegated responsibility involved in the study have adequate supervision, support and training.
- Appropriate arrangements are in place for obtaining informed consent for all participants including those who cannot give consent themselves
- If this is delegated to another member of the research team it is the PI responsibility to ensure this person has received adequate training to take informed consent
- The relevant healthcare professionals or care staff will be adequately informed of subjects' participation in the study

- Reports on the progress and outcomes of the work required by the R&I Department, the funder, research sponsor, REC and regulatory bodies are produced on time and to an acceptable standard
- Adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (drug) (SUSARs) must be reported according to the Medicines for Human Use (Clinical Trials) Regulations 2004
- Internal and external monitors/auditors are given access to documents, devices and equipment as necessary
- Arrangements are in place to archive the data when the research has finished, and to make it accessible. Records must normally be kept for 15 years

5 The Trainee Principal Investigator

5.1 The Role

A Specialty Registrar (StR) in Trauma & Orthopaedic Surgery who works with the local consultant PI for a research study and coordinates local trainee involvement. Trainees are extremely effective at engaging and recruiting patients into clinical trials, particularly during out-of-hours (evenings and weekends) when research teams are not present. Secondary to this is the requirement for you to be source of information and advice locally on Oxford Trauma trials for your Speciality Registrar (StR) colleagues.

5.2 The work

5.2.1 Recruitment

You will need to coordinate the recruitment of participants into trials, particularly during out-of-hours clinical practice. This doesn't mean you need to be in the hospital every weekend but you will need to ensure that the on-call StR is aware of the trial, the eligibility criteria, where the trial paperwork is kept, and the processes for recruiting and randomising participants into the trial.

Consent (see

5.2.2 Appendix 1 – Consent Patients for inclusion in Oxford Trauma Trials)

You will be required to obtain a patient's consent prior to entry into a trial. For many of our trials the consent process is complicated by the lack capacity and capability of trauma patients. The Mental Capacity Act (see below) allows for patients to be entered into a trial under a nominated consultee basis where 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 then being used to decide on the proper approach to consenting to the research. The clinical team will then provide guidance to the research team as to whether the patient has capacity to consent prospectively or if consultee agreement should be sought. This Nominated Consultee will be the patient's treating surgeon. If that surgeon is a member of the research team, another independent surgeon has to be identified. The Nominated Consultee will be asked, after reviewing the study documentation, to agree that the patient participate fully in the study and all trial procedures; this will be prospectively recorded during the electronic randomisation process. Further information regarding each trials' consent process are located within the protocols.

5.2.3 Randomisation

For Oxford Trauma trails randomisation is done online through https://rramp.octru.ox.ac.uk/. Each of our trials has a unique login and password per site. For many of our trials the time when a patient is randomised is paramount to the success of the trial. E.g. WHIST the patient inclusion criteria requires that a patient can only be randomised if the wound has been closed primarily, therefore, particularly for open fractures, randomisation can only occur at the end of surgery when the wound has been closed. Each trial protocol will provide you with this information.

5.3 Required Training & Knowledge & Documentation

5.3.1 Delegation of Duties

The clinical trials regulations state: "A sponsor of a clinical trial, in accordance with this regulation may delegate any or all of his functions under these regulations to any person but any such arrangement shall not affect the responsibility of the sponsor". The principle of delegation of duties is that the duty can be delegated but not the responsibility. This delegation may be from Sponsor to CI; CI to PI; PI to members of the site study team. At a study site, any duties that are delegated to the study team remain the responsibility of the PI. Each member of the team should perform their delegated duties adhering not only to research guidance and relevant legislation but also to local Trust and professional body requirements.

The PI can delegate duties, but never the responsibility for the study at the site. The allocation of duties to appropriately qualified persons should be recorded in a study specific delegation of duties log with specimen signatures and the initials of all involved. The recruitment and consent of patients into Oxford Trauma trials are delegated duties.

5.3.2 Good Clinical Practice & Curriculum Vitae

Evidence of appropriateness to perform the delegated duties is generally in the form of up to date Curriculum Vitae (CV), and evidence of Good Clinical Practice (GCP) training. GCP is the international ethical, scientific and practical standard to which all clinical research is conducted. Compliance with GCP provides public assurance that the rights, safety and wellbeing of research participants are protected and that research data are reliable.

The PI must be assured by these documents and knowledge of the study team that all team members are able to perform their delegated duties appropriately. You must also be aware of and compliant with any applicable regulatory requirements, e.g. Medicines for Human Use (Clinical Trials) Regulations 2004 or Research Governance Framework for health and social care 2005 (See Relevant Legislation & Guidance). You will need to ensure that your StR peers are also GCP trained- an efficient way to do this is to schedule it as part of a professional development or teaching session. Your research, development & innovation (RDI) department can help you identify GCP training locally. GCP training is also now a requirement for CCT in Trauma & Orthopaedic Surgery. It is recommended that your CV and GCP training should be updated every two years or when there is relevant change. These documents are essential documents and must be maintained as such within the study site file. Other training should be appropriate and proportionate to the type of research undertaken, and should cover the responsibilities of researchers set out in relevant legislation and standards. There is no set requirement for the frequency of such training. Researchers are expected to maintain awareness of current standards through reference to published guidance and relevant policies. Training should be updated when legislation has changed, new policies or practice have been implemented, different research activities are to be undertaken, or a significant period of time has elapsed since research activities have been conducted.

5.4 The Benefits

As the tPI you will be a named collaborator on the trial publication which adds to your list of publications. You can use it as part of the research requirements for CCT in Trauma & Orthopaedic Surgery[ii]. You will also gain valuable experience in trial processes which will be beneficial in your

consultant career. Furthermore, involvement in clinical trials can renew physicians' academic interchange with peers by encouraging participation in meetings, publications, and lecture series.

This is a new role that you can help to 'carve out'. We anticipate bringing the trainee PI group together once per year to share novel methods of recruitment and disseminating training at your hospital. We are also interested in hearing about your research ideas. There are doubtless many important questions that the trainee PI group can deliver.

6 Relevant Legislation & Guidance

6.1 Research Governance Framework for Health and Social Care (Department of Health, 2005)[iii]

The Research Governance Framework outlines principles of good governance that apply to all research within the remit of the Secretary of State for Health. Research governance is one of the core standards for health care organisations.

6.2 Mental Capacity Act[iv]

The Mental Capacity Act (MCA) is designed to protect and empower individuals who may lack the mental capacity to make their own decisions about their care and treatment. It is a law that applies to individuals aged 16 and over. Examples of people who may lack capacity include those with unconsciousness caused by an anaesthetic or sudden accident.

6.3 Medicines for Human Use (Clinical Trials) Regulations 2004[v]

The Medicines for Human Use (Clinical Trials) Regulations 2004, set out the legal requirements for pharmacovigilance in clinical trials involving UK participants. The regulations cover:

- Definitions of adverse events
- The responsibilities of investigators for recording of adverse events and the notification of adverse events to sponsors
- The responsibilities of sponsors for reporting to competent authorities and ethics committees, including expedited reports of SUSARs and annual safety reports.

To comply with the regulations, those taking on pharmacovigilance responsibilities must ensure that the necessary quality standards are observed in case documentation, data collection, validation,

evaluation, reporting and archiving of adverse events. This includes devising Standard Operating Procedures (SOPs) or equivalent written policies/guidelines.

6.4 HRA guidance on submission of curriculum vitae (CV)[vi]

The template documents are highly recommended for use. See link in references.

6.5 Data Protection Act 1998[vii]

The Data Protection Act 1998 (DPA) defines the law on the processing of data on identifiable living people and is the main piece of legislation that governs the data protection. In practice it provides a way for individuals to control information about themselves. The Act's definition of "personal data" covers any data that can be used to identify a living individual. Anonymised or aggregated data is not regulated by the Act, providing the anonymisation or aggregation has not been done in a reversible way. Individuals can be identified by various means including their name and address, telephone number or Email address. The Act applies only to data which is held, or intended to be held, on computers ('equipment operating automatically in response to instructions given for that purpose'), or held in a 'relevant filing system'.

In some cases even a paper address book can be classified as a 'relevant filing system', for example diaries used to support commercial activities, such as a salesperson's diary.

The Freedom of Information Act 2000 modified the act for public bodies and authorities.

The Data Protection Act creates rights for those who have their data stored, and responsibilities for those who store, process or transmit such data. The person who has their data processed has the right to:

- View the data an organisation holds on them. A 'subject access request' can be obtained for a nominal fee,
- Request that incorrect information be corrected,
- Require that data is not used in any way that may potentially cause damage or distress,
- Require that their data is not used for direct marketing.

6.6 Caldicott Guardians & Principles[viii]

Caldicott Guardians are the experts on confidentiality issues and access to patient records who are on-site to give you advice on any concerns that you may have about a case. The 'Caldicott' principles and recommendations apply specifically to patient-identifiable information, and emphasise the

need for controls over the availability of such information and access to it. In particular, a Caldicott Guardian, appointed in each NHS organisation, has specific responsibilities to oversee an ongoing process of audit, improvement and control.

The six Caldicott principles, applying to the handling of patient-identifiable information, are:

- justify the purpose(s) of every proposed use or transfer
- don't use it unless it is absolutely necessary, and
- use the minimum necessary
- access to it should be on a strict need-to-know basis
- everyone with access to it should be aware of their responsibilities, and
- understand and comply with the law.

Appendix 1 – Consent Patients for inclusion in Oxford Trauma Trials

The usual situation for gaining consent in clinical trials reflects what we are used to in routine clinical practice before surgery. You will determine the mental capacity of the patient – that is, their ability to receive, understand and weigh information and communicate a decision. Patients with capacity will then give voluntary, informed consent for a treatment based upon the advice received prior to the procedure.

However, in many emergency situations, the patient's capacity may limited by their environment, their injury, it's treatment , and the use of opioid analgesia. Conducting research in this 'emergency setting' is regulated by the Mental Capacity Act 2005 (MCA). If the patient lacks capacity, you should act in accordance with section 32, subsection 9b of the MCA following a process approved by the relevant research ethics committee.

The appropriate method for entering a patient into the trials is described below. There are three possible scenarios as follows:

The patient has capacity before surgery

Where you judge that prospective patient consent is appropriate, you or a member of the research team should approach the patient for their informed consent before surgery.

The patient does not have capacity before surgery - family members or carers (personal consultees) are available

If you believe that prospective patient consent is not appropriate, you should approach an appropriate Consultee. Where a Personal Consultee is available (i.e. family member or carer), they will be provided with the study information. The Personal Consultee will be given the opportunity to ask questions and discuss the study, after which their written agreement should be recorded.

The patient does not have capacity before surgery - family members or carers (personal consultees) are not available

Where a Personal Consultee is not available then a Nominated Consultee should be identified. The Nominated Consultee may be the surgeon or another member of the clinical team treating the patient. If you or that other surgeon is a member of the research team i.e. the Principal Investigator or Trainee Principal Investigator, another independent surgeon should be identified. The Nominated Consultee will be asked, after reviewing the patient, to agree that the patient participate fully in the

study and all trial procedures; this will be prospectively recorded during the electronic randomisation process.

It is important to note that you should record your decision to act as a Nominated Consultee in the medical notes. You/the Nominated Consultee should provide a wet-ink signature on a copy of the electronic recorded agreement at the first appropriate opportunity and when the clinical situation allows. The local Research nurse or other member of the research team will usually organise this signature.

Patients who regain capacity after surgery

For those patients that did not consent prior to surgery, the research team will provide the patients with all of the study information at the first appropriate time when the patient has regained capacity. The patients will be given the opportunity to ask questions and discuss the study with their family and friends. They will then be asked to provide written consent for continuation in the study.

Patients with permanent lack of capacity

For those patients who did not prospectively consent or who had a Nominated Consultee give prospective agreement and still lack capacity after their surgery, every effort will be made to contact a Personal Consultee to advise the research team about the patients continued participation in the study. The Personal Consultee will be provided with all the study information and be given the opportunity to ask questions and discuss the study with other relatives and friends.

If no Personal Consultee can be identified, the patient will remain in the study under the Nominated Consultees agreement provided at the time of enrolment.

Responsibility for recording and dating both the definitive written informed consent or agreement will be with the investigator, or persons delegated by the investigator, who conducted the informed consent discussion. Delegated responsibility should be recorded on the site delegation log.

For further details, please read:

Costa ML, Tutton E, Achten J, Grant R, Slowther AM.
Informed consent in the context of research involving acute injuries and emergencies.
Bone Joint J. 2017 Feb;99-B(2):147-150

7.2.9.3 EnTraP Trainee Pi checklist

Appendix 2 – Checklist for new trainee PIs

New Trainee Principal Investigator Checklist

INFORMATION

Name: Start date:

Principal Investigator(s):

Trials:

FIRST DAY

Receive role and responsibilities

Meet Research Associates

DOCUMENTS

Review key documents.

- Trial Protocols
- Trial Consent forms
- Trial Patient information leaflets
- Trial Specific Instructions
- Trial CRFs
- SAE reporting guidelines

ADMINISTRATIVE PROCEDURES

Review administrative procedures.

- Complete Site Delegation
- Locate RRAMP login details

LOCATIONS

Aware of location of Investigator Site File

POSITION INFORMATION

Introduction to team of new role

REQUIREMENTS

The following is a handy list of the requirements of a PI:

- Overall responsibility for study at site

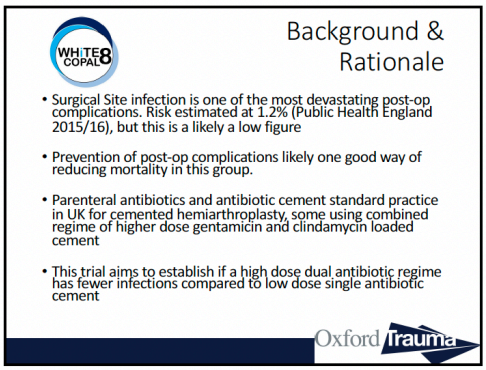
- Medical care and supervision of patients
- Delegation of study related duties
- Ensuring all staff delegated to work on trial are adequately informed as to protocol
- requirements and trained in study procedures
- Familiarity with Investigator Brochure (where available)
- Patient recruitment strategy
- Screening of patients
- Informed consent
- Signing of consent form (as appropriate to local policy & practice)
- Randomisation (as appropriate to local policy & practice)
- Administration of investigational product (if applicable)
- Collection of trial related blood samples (if applicable)
- Completion and return of Case Record Forms and providing responses to data queries
- Documentation of adverse events
- Timely Serious Adverse Events reporting
- Initiation of new trial personnel
- Available for audit and inspections
- Archiving of study documentation

7.2.9.4 EnTraP Trainee Pi Induction presentation

WHiTE 8 COPAL SIV Training Presentation

1

2



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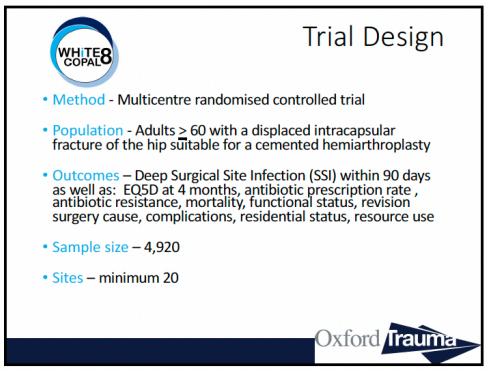

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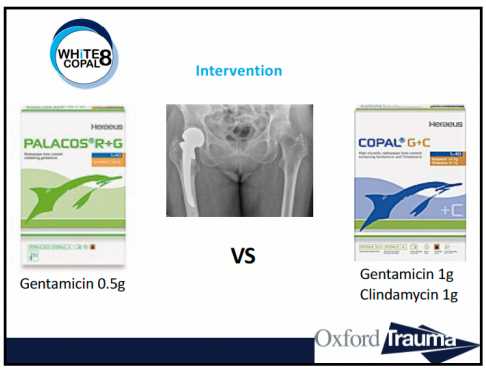

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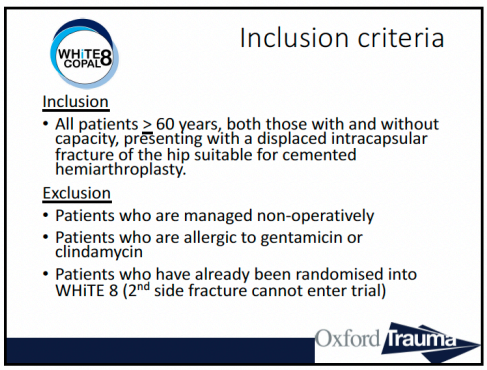

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Trainee PIs

- A specially nominated trainee who works with the local consultant PI
- Primary role is to coordinate local trainee involvement in identifying, consenting and randomising patients to the study
- Also act as a source of information, advice and train trainees regarding trial procedure locally
- Ensure that you are GCP trained and have an up to date research CV

Oxford Trauma

8

TPI suggestions

- Introduce yourself to the local Principal Investigator and the Orthopaedic Research nurses
- Familiarise yourself with the location of the WHiTE 8 Site file
- Familiarise yourself with the trial documentation that need to be completed
- Make yourself known to the department (consultants and trainees) as the WHiTE 8 TPi

Oxford Trauma

9

TPI suggestions

- Organise a research induction with trainees and research nurse for patient recruitment guidance
- Ensure that everyone has GCP and facilitate GCP training for those who do not have it
- Targeted reminders to colleagues by email, text, WhatsApp to recruit to the WHiTE 8 trial prior to on call shifts.
- Attend trauma meetings or delegate this responsibility in order go find eligible patients
- Liaise with research nurses regularly to review recruiting performance

Oxford Trauma

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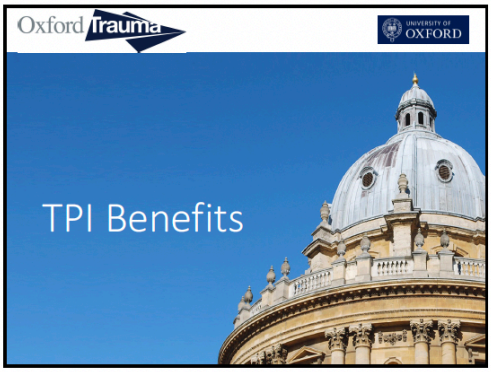

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TPI benefits

- Collaborator on trial publication
- Evidence as Leadership & Management requirement for ARCP and CCT
- Evidence as Research requirements for ARCP and CCT
- Experience in a trial that can be used in your future consultant career to become a local Principal Investigator

Oxford Trauma

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Guidelines

- Prospective agreement should be sought from patient, personal consultee, or nominated consultee
  - Capacity – determined with the clinical care team
  - Determine appropriateness of approaching personal consultee (if present) before surgery
- Retrospective consent/agreement should be sought if a patient regains capacity or nominated consultee used

Oxford Trauma

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Information Sheets

- Patient Information Sheet
  - Prospective
  - Retrospective
- Consultee Information Sheet
  - Prospective
  - Retrospective
- Patient/Consultee Invitation Letter
  - Last resort (REC Recommendation) when participant discharged without obtaining consent. Available from the Trial Office on request.

Oxford Trauma

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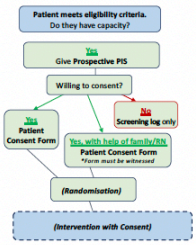
Patients with capacity



- Prospective patient information sheet
- Patient consent form (can be witnessed)
- After surgery: no action needed

Oxford Trauma

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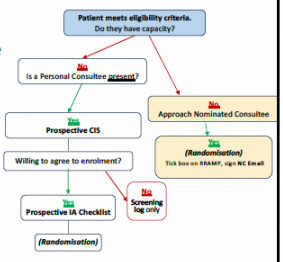
Patients without capacity

- Prospective consultee information sheet
- Consultee informed agreement *or* nominated consultee signs email
- After surgery: additional action needed



Oxford Trauma

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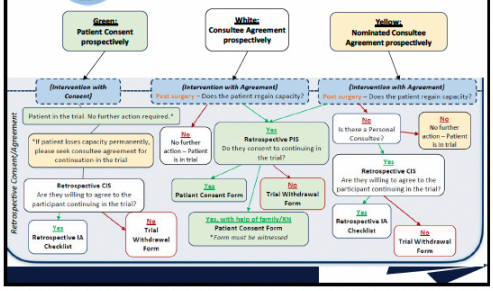
After surgery



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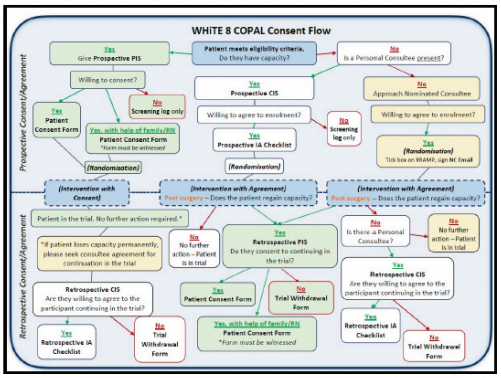

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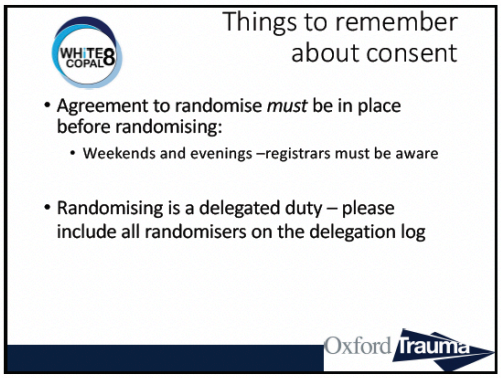

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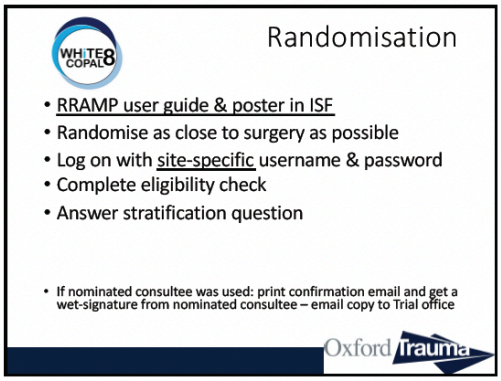

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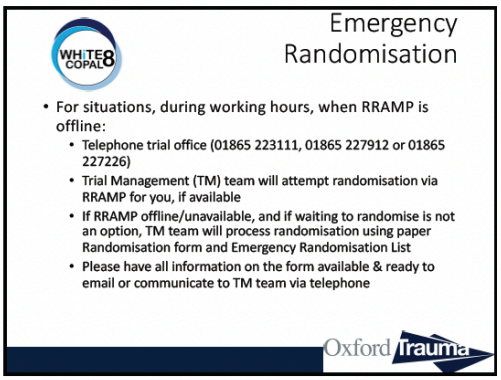

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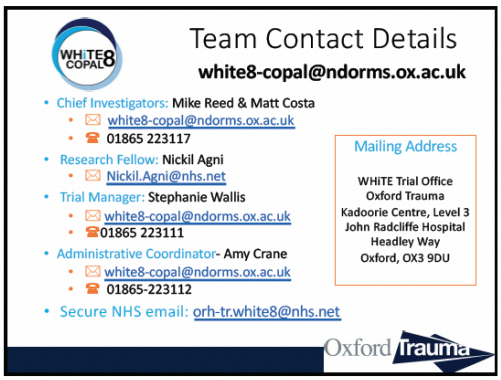

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7.2.10 EnTraP Trainee Pi supplementary information

7.2.10.1 SWAT participation information

UNIVERSITY of York
The Department of Health Sciences

The use of an Enhanced Trainee Principal Investigator intervention in the WHiTE 8 COPAL Randomised Control Trial

Participant Information Sheet

We would like to invite you to take part in the above study:

What is the purpose of this study?
Trainee Principal investigators (TPi) are training orthopaedic registrars whose role is to work alongside local consultant principal investigators in a research study. The principal aim of the role is to coordinate and engage local trainees in recruiting patients to the trial especially outside of normal working hours. Several multicentre orthopaedic trials have utilised trainee principal investigators at recruitment centres, however the effects on recruitment rates have not been formally evaluated or published.

The enhanced TPi role is a package of education and peer support in order for you to better deliver the role as a trainee principal investigator in your hospital.

Who is doing the study?
The study is being run by Mr Nickil Agni who is an Orthopaedic Surgeon in Training based at the University of York Trials Unit, currently working with the Oxford Clinical trials unit to deliver the WHiTE 8 COPAL trial. The York Trials Unit is sponsored by the British Orthopaedic Association to develop and expand the portfolio of trials in the UK related to trauma and orthopaedics. This work is being completed as part of an PhD project at York University.

Who is being asked to participate?
Trainee Principal Investigators who are affiliated with WHiTE recruiting centres that have been randomly allocated to receiving this intervention.

Do I have to take part?
You have volunteered to participate as a Trainee Principal Investigator for the WHiTE 8 COPAL trial. A package of education and on-going support is part of this role in your hospital. It is regrettable, but you are well within your right to decline this role. Please let the WHiTE 8 Research fellow (Nickil Agni) know at the earliest opportunity if you wish to not be involved in this study so that another suitable TPi can be recruited to your WHiTE trial centre.

What will be involved if I take part in this study?
You will receive a 1:1 telephone training session delivered at your convenience and an emailed package of material. At the end of your time as a TPi we will ask you to participate in a survey of your experience so that we can suitably improve this role for future trainees.

What are the advantages/benefits and disadvantages/risks of taking part?
All Trainee Principal investigators at WHiTE centres will be included as collaborators on output related to WHiTE 8 Copal RCT. Evidence of leadership and management for ARCP, experience of some of the duties of a Principal Investigator and experience in multicentre RCT research are also benefits of becoming a TPi.

The data collected with regards to your participation will also inform future decisions regarding how best to deliver TPi training and improve the satisfaction of the trainee during his/her period in the role.

Can I withdraw from the study at any time?

You can withdraw from being a TPi at any point, but we urge you to let the local Principal Investigator and the WHiTE 8 research fellow (Nickil Agni) aware regarding this at the earliest possible point so a suitable replacement can be instructed.

Will the information obtained in the study be confidential? *or* Will the information I give be kept confidential?

There will be no participant identifiable material collected other than your contact information for communication through WhatsApp, SMS, Telephone and email for ongoing peer support, conflict resolution and survey purposes. No patient related material will be communicated through the above communication methods.

We will keep all email addresses and telephone numbers confidential, and these will not be distributed by the Oxford CTU or York University to any third parties. Survey responses will be anonymous, and no participant linked information will be collected.

What will happen to the results of the study?

The results of the study will be used as part of a PhD thesis and any research output related to this will be sent to all trainee principal investigators to inform them of the conclusions drawn from the study.

Who has reviewed this study?

The research has been approved by the Department of Health Sciences' Research Governance Committee at the University of York. Ethics Approval ID: **HSRGC/2018/266/C**

Who do I contact in the event of a complaint?

If you have any concerns please contact Dr Catriona McDaid (Reader in Trials and Research Supervisor) Tel: +44 (0)1904 321371 Email: catriona.mcdaid@york.ac.uk

If you agree to take part, would like more information, or have any questions or concerns about the study please contact

Mr Nickil Agni MBBS, BSc, MRCS, Orthopaedic Registrar in Training Northern Deanery, Research Fellow WHiTE 8 Copal trial.

ARRC Building, York Trials Unit, Department of Health Sciences, University of York, Heslington, YO10 5DD. Nra513@york.ac.uk. Tel: +44 (0)1904 321371

Thank you for taking the time to read this information

7.2.10.2 EnTraP Trainee Pi consent for contact during the trial

UNIVERSITY of York
The Department of Health Sciences

WHiTE 8 COPAL Randomised Control Trial

TPi Contact information

Thank you for participating in this study. The contact information you provide will be used only in relation to communication regarding the trial. This information will be kept confidential and not be distributed to third parties:

Trainee Principal Investigator:	
Email Address:	
Mobile number:	

I consent to the information above being used to:

- **Keep updated regarding trial specific matters** ☐
- **Form a TPi WhatsApp group for ongoing communication** ☐
- **Send evidence of participation as a TPi in the WHiTE 8 COPAL trial.** ☐

Signed:

Date:

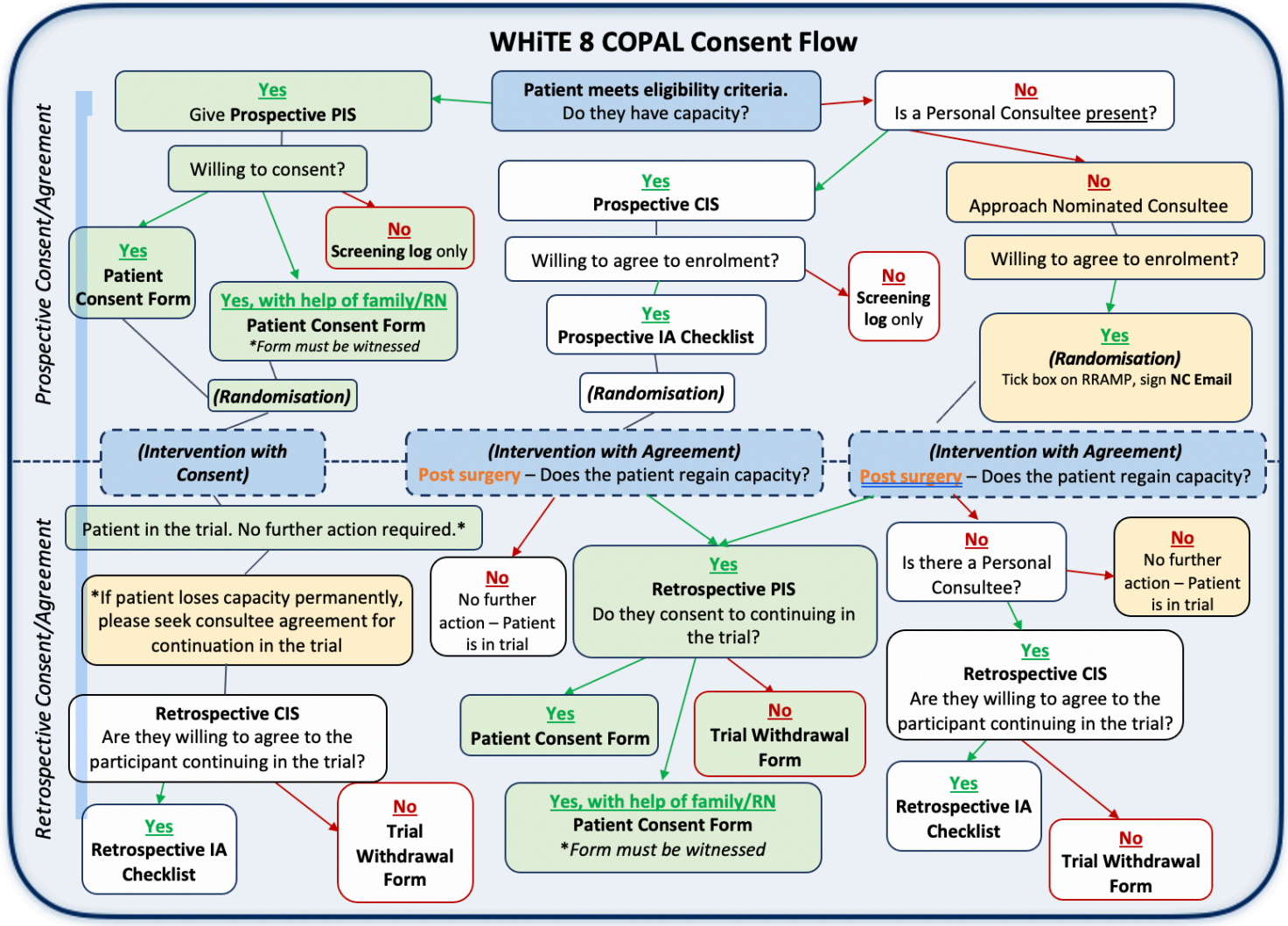
If you agree to take part, would like more information, or have any questions or concerns about the study please contact

Mr Nickil Agni MBBS, BSc, MRCS, Orthopaedic Registrar in Training Northern Deanery, Research Fellow WHiTE 8 Copal trial.

ARRC Building, York Trials Unit, Department of Health Sciences, University of York, Heslington, YO10 5DD. Nra513@york.ac.uk. Tel: +44 (0)1904 321371

Thank you for taking the time to complete this information

7.2.10.3 EnTraP TPi consent flow chart to recruit to WHiTE 8 trial



WHiTE 8 Consent Flow Diagram V1.1 – 11 June 2018

Document Name	File Name	Function
Prospective Patient Information Sheet (PIS)	WHiTE8_ProspPIS	To be given to patients who have capacity before their surgery, to inform them of the WHiTE 8 COPAL trial before seeking consent for participation.
Prospective Consultee Information Sheet (CIS)	WHiTE8_ProspCIS	To be given to a personal consultee before a patient's surgery, to inform them of the WHiTE 8 COPAL trial before seeking consultee agreement for the patient's participation.
Retrospective Patient Information Sheet (PIS)	WHiTE8_RetroPIS	To be given to patients who have regained capacity after their surgery, to inform them of the WHiTE 8 COPAL trial before seeking consent for continued participation in the trial.
Retrospective Consultee Information Sheet (CIS)	WHiTE8_RetroCIS	To be given to a personal consultee after a patient's surgery, in the case where a PC was not present before and a patient has not regained capacity, to inform them of the WHiTE 8 COPAL trial before seeking consultee agreement for the patient's participation.
Patient Consent Form	WHITE8_PatientConsentForm	To be given to a patient after they have read through the PIS, have had the opportunity to ask questions and are satisfied they can make an informed decision of consent. Patient must initial each box and sign at the bottom. **If this forms is being filled out by a personal consultee for a patient, it must be witnessed.*
Prospective Informed Agreement (IA) Checklist	WHiTE8_ProspIAChecklist	To be given to a personal consultee (before the surgery), after they have read through the CIS, have had the opportunity to ask questions and are satisfied they can make an informed decision of agreement.
Retrospective Informed Agreement (IA) Checklist	WHiTE8_RetroIAChecklist	To be given to a personal consultee (after the surgery), after they have read through the CIS, have had the opportunity to ask questions and are satisfied they can make an informed decision of agreement.

7.2.11 EnTraP digital nudge proforma

To be sent to the randomiser:

Dear (***insert first name***),

(***Encouragement Word– random from table 1***) for randomising (***subject(s) W8 -xxxxx***) to the WHiTE 8 COPAL trial.

(***Statement of appreciation – random from table 2***) in recruiting this/these patient(s) to the trial as we understand the difficulty and pressures of accommodating this during your busy day.

Your participation gets us one step closer to the target sample size of 4920 patients and we would be grateful if you would continue to recruit patients as the opportunity arises,

Keep up the good work,

Nickil Agni (digital sign off)
Mike Reed (digital sign off)

Table 1: Encouragement words

Brilliant work	Incredible work
Excellent job	Outstanding job
Superb job	Tremendous work
Fantastic work	Awesome job
Amazing job	Exceptional job

Table 2: Statement of appreciation

We thank you for your effort
We appreciate your commitment
We thank you for your hard work
We appreciate your effort
We value your contribution
We highly regard your contribution

7.3 Systematic review appendix

7.3.1 Prospero protocol for systematic review

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

The incidence of prosthetic joint infection when using antibiotic loaded bone cement in fracture neck of femur patients receiving a hermiarthroplasty

Citation

Nickil Agni, Catriona McDaid, David Torgerson, Mike Reed. The incidence of prosthetic joint infection when using antibiotic loaded bone cement in fracture neck of femur patients receiving a hermiarthroplasty. PROSPERO 2022 CRD42022360341 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022360341

Review question

1. Is antibiotic loaded cement better than plain cement at preventing deep infection in patients undergoing a hip hemiarthroplasty for a neck of femur fracture?

2. Is dual antibiotic loaded cement better than single antibiotic loaded cement at preventing deep infection in patients undergoing a hip hemiarthroplasty for a neck of femur fracture?

Searches

The Electronic databases to be searched include:

• The Cochrane Controlled Register of Trials (CENTRAL)

• Ovid MEDLINE

• Embase

• ISI Web of Science: Science Citation Index

• ClinicalTrials.gov

• Current Controlled Trials

• WHO International Clinical Trials Registry Platform (ICTRP) Search Portal

There will be no restriction on language or publication date and searches will be inclusive till 1/10/22

Types of study to be included

Studies included will be all randomised control trials (RCT), quasi-randomised and nonrandomised studies with a control group comparing antibiotic loaded cement to either another concentration of antibiotic loaded bone cement or plain bone cement. Non-English language studies will also be included if suitable translations can be acquired.

Studies with no control group will be excluded.

Condition or domain being studied

Antibiotic loaded cement in hip hemiarthroplasty

Participants/population

All patients receiving a cemented hip hemiarthroplasty for an intracapsular neck of femur fracture. We will include studies with participants receiving all types of cemented hemiarthroplasties designs using any surgical approach and any combination of perioperative oral/parenteral prophylactic antibiotic therapy.

Studies that include cemented hemiarthroplasties for fracture as a subgroup will also be included so long as data can be extracted separately.

Participants receiving elective total hip and total knee replacements and emergency total hip replacements will be excluded. Revision cases and surgery in the context of active hip infection will be excluded.

Intervention(s), exposure(s)

The intervention will be the intraoperative use of antibiotic loaded cement when performing a cemented hemiarthroplasty for an intracapsular neck of femur fracture.

We will include studies with any dose and combination of antibiotic loaded cement either in pre-formulated preparations or self-manufactured during surgery.

Comparator(s)/control

Eligible comparators will be a group with differing doses of bone cement, either single antibiotic or plain bone cement.

Main outcome(s)

Deep infection rate at surgical site

Measures of effect

We will include studies that report follow up of hip hemiarthroplasty patients that reports infection outcomes. The classification system for deep infection and follow up duration will not be specified as to maximise search results.

Additional outcome(s)

Any validated measure of quality of life, mortality, rates of complication and antibiotic resistance profiles.

Data extraction (selection and coding)

Covidence software for systematic reviews will be used to store and manage data.

Study selection will be conducted by two independent reviewers. Titles and abstracts will be reviewed to assess eligibility against predetermined criteria. Full papers of potential eligible studies will be obtained and screened using the same methodology. A third reviewer will be consulted when consensus cannot be reached. Authors of eligible studies will be contacted to provide additional information where necessary. Additionally, in the case of multiple publications, the study with the most up-to-date or comprehensive information will be included.

Data will be extracted by one author using a standardised data extraction form and present information in a "Characteristics of included studies" and result table. This will be checked by the second author and only involve the third author if consensus is not achieved. Information extracted will include where available, study design, publication date, geographical location, mean age, co-morbidities, type of bone cement, duration of follow-up, sample size, number of deep infection events, risk estimates.

Risk estimates will be calculated for studies that report counts and when this cannot be calculated study authors will be approached to calculate estimates.

Risk of bias (quality) assessment

Two reviewers will independently assess the risk of bias and qualities of studies included. For randomised control trials we will use the Cochrane Risk of Bias tool. Non-randomised, cohort studies and case-control studies will be assessed based on the nine-star validated Newcastle-Ottawa Scale (NOS). It uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest.

Strategy for data synthesis

Tables of study characteristics and results will be presented with a narrative description of the included studies. Clinical and Methodological heterogeneity will be considered. Clinical heterogeneity will be assessed at patient level (e.g., age, gender and comorbidities), intervention level (e.g. ALBC dose, preparation method, brand and use of additional parenteral antibiotics), Outcome level (e.g. timing of measurement, follow up length). Assessment of methodological heterogeneity will include factors such as blinding, allocation differences, outcome definition and measurement etc.

Odds ratios will be used as the common measure of association across studies. Forest plots will be used to examine the data and pooling of outcomes will be conducted if appropriate using a random effects model. Statistical heterogeneity will be assessed using the Cochran χ^2 statistic and the I^2 statistic if feasible.

If statistic pooling is not thought to be useful due to heterogeneity of studies then findings will be presented in the narrative review using figures and tables as appropriate. This protocol and final systematic review will be reported in line with the PRISMA-P 2015 checklist.

Analysis of subgroups or subsets

There will be no specified subgroup analysis outside of those outlined as the aims of this systematic review.

Contact details for further information

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Mr Mike Reed. Northumbria Healthcare Foundation Trust

Type and method of review

Systematic review

Anticipated or actual start date

01 October 2022

Anticipated completion date

01 February 2023

Funding sources/sponsors

Not applicable

Conflicts of interest

None known

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Anti-Bacterial Agents; Bone Cements; Femoral Neck Fractures; Femur; Hemiarthroplasty; Humans; Incidence

Date of registration in PROSPERO

04 November 2022

Date of first submission

03 November 2022

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

04 November 2022

7.3.2 Systematic review search strategy

An example of search strategy is outlined below for:

Medline and Embase via Ovid

Embase <1974 to 2022 November 09>
Ovid MEDLINE(R) ALL <1946 to November 09, 2022>

1 exp prosthesis-related infection/ 26176
2 exp bone cement/ 41418
3 exp hemiarthroplasty/ 4654
4 exp femoral neck/ 16104
5 exp arthroplasty, replacement, hip/ 47908
6 antibiotic loaded bone cement.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy] 448
7 antibiotic-laden.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy] 204
8 antibiotic impregnated.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy] 1965
9 dual antibiotic.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy] 306
10 exp surgical wound infection/ 97259
11 exp copal/ 1383
12 1 or 10 121895
13 2 or 6 or 7 or 8 or 9 or 11 44698
14 3 or 4 or 5 66074
15 12 and 13 and 14 421

Web of science

Web of Science Search Strategy (v0.1)
Database: Web of Science Core Collection
Entitlements:
- WOS.SSCI: 1956 to 2022
- WOS.AHCI: 1975 to 2022
- WOS.ISTP: 1990 to 2022
- WOS.ESCI: 2015 to 2022
- WOS.SCI: 1900 to 2022
- WOS.ISSHP: 1990 to 2022
Searches:
1: ((ALL=(prosthetic joint infection)) OR ALL=(surgical wound infection)) OR ALL=(prosthesis-related infection) Date Run: Thu Nov 10 2022 19:15:16 GMT+0000 (GMT) Results: 28233
2: (((((ALL=(bone cement)) OR ALL=(antibiotic loaded bone cement)) OR ALL=(antibiotic-laden)) OR ALL=(antibiotic impregnated)) OR ALL=(dual antibiotic)) OR ALL=(copal) Date Run: Thu Nov 10 2022 19:16:49 GMT+0000 (GMT) Results: 25443
3: (((ALL=(hemiarthroplasty)) OR ALL=(femoral neck)) OR ALL=(hip replacement)) OR ALL=(arthroplasty, replacement, hip) Date Run: Thu Nov 10 2022 19:18:35 GMT+0000 (GMT) Results: 68931
4: #3 AND #2 AND #1 Date Run: Thu Nov 10 2022 19:18:44 GMT+0000 (GMT) Results: 179

7.3.3 Newcastle Ottawa scale study assessment

The rationale for each studies score is summarised as follows:

Aedo-Martin et al (2019)

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort	
a) truly representative of the average, elderly, community-dwelling resident	★
b) somewhat representative of the average, elderly, community-dwelling resident	★
c) selected group of patients, e.g., only certain socio-economic groups/areas	
d) no description of the derivation of the cohort	
2. Selection of the non intervention cohort	
a) drawn from the same community as the intervention cohort	★
b) drawn from a different source	
c) no description of the derivation of the non intervention cohort	
3. Ascertainment of intervention	
a) secure record (e.g. health care record)	★
b) structured interview	★
c) written self report	
d) other / no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for age, sex, marital status	★
b) study controls for any additional factors (e.g. socio-economic status, education)	★
Outcome (tick one box in each section)	
1. Assessment of outcome	
a) independent blind assessment	★
b) record linkage	★
c) self-report	
d) other / no description	
2. Was follow up long enough for outcomes to occur	
a) yes, if median duration of follow-up >= 6 month	★
b) no, if median duration of follow-up < 6 months	
3. Adequacy of follow up of cohorts	
a) complete follow up: all subjects accounted for	★
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	★
c) follow up rate < 80% (select an adequate %) and no description of those lost	
d) no statement	

Assessment of quality of this cohort study achieved a total score of six. Within the category of "selection" the study achieved two points. The intervention and non-intervention cohort were derived

from the same population; however, this was a selected population and unlikely representative of the average hip fracture patient in the community. Patients were identified from health records (national hip database) and SSI was not present at the start of the study as surgery had not occurred.

The study scored two points for comparability between cohorts as the study identified baseline characteristics of sex and age and additional other factors such as energy of mechanism and risk factors for infection between both intervention and non-intervention cohort.

There was health record reported outcomes however no minimum follow up time or statement on loss to follow up was made and therefore no additional points scored.

Sanz-Ruiz et al (2016)

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort	
a) truly representative of the average, elderly, community-dwelling resident	★
b) somewhat representative of the average, elderly, community-dwelling resident	★
c) selected group of patients, e.g., only certain socio-economic groups/areas	
d) no description of the derivation of the cohort	
2. Selection of the non intervention cohort	
a) drawn from the same community as the intervention cohort	★
b) drawn from a different source	
c) no description of the derivation of the non intervention cohort	
3. Ascertainment of intervention	
a) secure record (e.g. health care record)	★
b) structured interview	★
c) written self report	
d) other / no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for age, sex, marital status	★
b) study controls for any additional factors (e.g., socio-economic status, education)	★
Outcome (tick one box in each section)	
1. Assessment of outcome	
a) independent blind assessment	★
b) record linkage	★
c) self report	
d) other / no description	
2. Was follow up long enough for outcomes to occur	
a) yes, if median duration of follow-up >= 6 month	★
b) no, if median duration of follow-up < 6 months	
3. Adequacy of follow up of cohorts	
a) complete follow up: all subjects accounted for	★
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	★
c) follow up rate < 80% (select an adequate %) and no description of those lost	
d) no statement	

Assessment of quality of this cohort study achieved a total score of eight. Within the category of "selection" the study achieved three points. Although the intervention and non-intervention cohort were derived from the same population, they were not representative of the overall population of hip fractures. Only the patients with poor bone which is often a surrogate marker of frailty were selected to have cemented partial hips. Patients were identified from health records and SSI was not present at the start of the study as surgery had not occurred.

The study scored two points for comparability between cohorts as the study controlled not only for age and gender but also for co-morbidity and ASA score.

There was health record reported outcomes with minimum follow up duration of two years and <20% loss to follow up

Tyas et al (2018)

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort	
a) truly representative of the average, elderly, community-dwelling resident	★
b) somewhat representative of the average, elderly, community-dwelling resident	★
c) selected group of patients, e.g., only certain socio-economic groups/areas	
d) no description of the derivation of the cohort	
2. Selection of the non intervention cohort	
a) drawn from the same community as the intervention cohort	★
b) drawn from a different source	
c) no description of the derivation of the non intervention cohort	
3. Ascertainment of intervention	
a) secure record (e.g. health care record)	★
b) structured interview	★
c) written self report	
d) other / no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for age, sex, marital status	★
b) study controls for any additional factors (e.g., socio-economic status, education)	★
Outcome (tick one box in each section)	
1. Assessment of outcome	
a) independent blind assessment	★
b) record linkage	★
c) self report	
d) other / no description	
2. Was follow up long enough for outcomes to occur	
a) yes, if median duration of follow-up >= 6 month	★
b) no, if median duration of follow-up < 6 months	
3. Adequacy of follow up of cohorts	
a) complete follow up: all subjects accounted for	★
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	★
c) follow up rate < 80% (select an adequate %) and no description of those lost	
d) no statement	

Assessment of quality of this cohort study achieved a total score of five. Within the category of "selection" the study achieved four points. The patient population involved in the study, (both intervention and non-intervention cohort), were representative of the average patient presenting with a neck of femur fracture. There was no selection bias as all patients presenting to the single NHS trust

were included retrospectively from secure health care records. Additionally, a point was given for demonstration that SSI was not present at the start of the study. Although there was no statement regarding this, the nature of the outcome of interest is that it could not be present pre-operatively as SSI only occurs after surgical intervention. The study did not assess and control for differences between intervention and non-intervention patients and thus no point was awarded.

When considering the scoring for “Outcome” one point were achieved. The assessment of outcome was ascertained from heath records, however the minimum follow up time was not stated. The definition of SSI used was from Public Health England which attributes a timeframe of within one year however it would be an assumption that this time frame was followed. Hence no score was given for this section of “Outcome”. There was also no statement on loss to follow up.

Savage et al (2019)

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort	
a) truly representative of the average, elderly, community-dwelling resident	★
b) somewhat representative of the average, elderly, community-dwelling resident	★
c) selected group of patients, e.g., only certain socio-economic groups/areas	
d) no description of the derivation of the cohort	
2. Selection of the non intervention cohort	
a) drawn from the same community as the intervention cohort	★
b) drawn from a different source	
c) no description of the derivation of the non intervention cohort	
3. Ascertainment of intervention	
a) secure record (e.g. health care record)	★
b) structured interview	★
c) written self report	
d) other / no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for age, sex, marital status	★
b) study controls for any additional factors (e.g., socio-economic status, education)	★
Outcome (tick one box in each section)	
1. Assessment of outcome	
a) independent blind assessment	★
b) record linkage	★
c) self report	
d) other / no description	
2. Was follow up long enough for outcomes to occur	
a) yes, if median duration of follow-up >= 6 month	★
b) no, if median duration of follow-up < 6 months	
3. Adequacy of follow up of cohorts	
a) complete follow up: all subjects accounted for	★
b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, or description of those lost suggesting no different from those followed	★
c) follow up rate < 80% (select an adequate %) and no description of those lost	
d) no statement	

Assessment of quality of this cohort study achieved a total score of three. Within the category of "selection" the study achieved two points. It is not clear if the intervention and non-intervention cohort were derived from the same population. Also, the study period is not defined and thus it unclear if the hip fractures included in this study were representative of the overall population of hip fractures. Patients were identified from health records (national hip database) and SSI was not present at the start of the study as surgery had not occurred.

The study scored zero points for comparability between cohorts as the study did not account for any differences between both intervention and non-intervention cohort.
There was health record reported outcomes within one year of surgery, but there is no defined minimum follow. up period or statement on loss to follow up and therefore no additional points scored.

7.3.4 Revised Cochrane risk-of bias tool assessment

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group
Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details	
Reference	Agni et al – White 8

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Copal G+C Comparator: Palacos R+G

Specify which outcome is being assessed for risk of bias	Primary deep SSI rate
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Primary: 1.43, 95% CI 0.87 to 2.35, Per protocol 1.52, 95% CI 0.89 - 2.58, As treated: 1.6, 95% CI 0.95 - 2.71).

Is the review team's aim for this result…?

■ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

■ Journal article(s) with results of the trial
■ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)

☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Only unblinded to surgical team performing the operation but blind to research nurses collecting data post operatively. Unlikely to contribute to bias	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Protocol deviations not categorised	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Only unblinded to surgical team performing the operation but blind to research nurses collecting data post operatively. Unlikely to contribute to bias	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		Y
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		Y
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Sample size inflated to account for missing data by 16%. Missing data was lower than this rate so there was no consequence from the missing data	PN
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		Y
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group
Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	Sprowsen et al

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Copal G+C Comparator: Palacos R+G

Specify which outcome is being assessed for risk of bias	Deep surgical site infection
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	13/376 (3.5%) deep SSI in LDSAC, 4/360 (1.1%) in HDDAC. Adjusted Intention to treat: 0.31, 95% CI 0.09 to 0.88. Adjusted Per Protocol: 0.33, 95% CI 0.09 to 0.95

Is the review team's aim for this result…?

■ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

■ Journal article(s) with results of the trial
■ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial

☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Stratified quasi randomisation as per study centre on an alternative monthly basis.	PN
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No allocation sequency used due to randomisation strategy, but unlikely to have an effect as randomisation allocation could not be subverted.	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement	Some concerns from randomisation strategy however both intervention and control group were affected equally. Formal tests showed no differences in baseline characteristics	Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Surgeons aware but research nurses unaware	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	<6% loss to follow up in both groups. Mote loss to follow up in control group.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Sensitivity analysis performed for data exclusions (deaths within 30 days)	PY
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Fixed effects analysis done rather than random effect as per protocol	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement	As described in randomisation section	Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA

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