Management of Periprosthetic Hip and Knee Joint Infections after Lower Limb Arthroplasty

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Declaration

I, Mohamed Sukeik, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. Colleagues acknowledged were part of the teams I led and their contributions included assisting in performing the literature reviews and conducting the randomised controlled trial.

Mohamed Sukeik  November 2016

Abstract

Introduction

Infection after lower limb arthroplasty is a serious complication with significant consequences for both patients and healthcare systems. Management is often challenging and frequently leads to a suboptimal functional outcome. Revision surgery remains a very expensive procedure to the patient and healthcare systems and no matter how much progress in diagnostic and treatment methods are achieved, the cost and morbidity of infected cases suggest that preventative measurements are the single most important factor in managing this problem. On the other hand, tertiary referral centres with well established strategies for treatment of infections may improve the rates of eradicating infection and overall outcomes. Therefore, the hypothesis of this thesis was that preventative and management strategies undertaken will improve the outcome of infection control. Studies included focused on prevention of infection but also explored the strategies and novel approaches implemented at University College London Hospital to improve the outcome of eradicating infection after hip and knee arthroplasties.

Materials and Methods

A comprehensive review of the current literature was initially conducted. This was followed by a number of studies to investigate prevention and treatment strategies of periprosthetic hip and knee joint infections:

a) A randomised controlled trial has been conducted to compare postoperative wound complications of triclosan impregnated sutures and conventional non-coated sutures in patients undergoing primary hip and knee arthroplasties. Triclosan has been shown to reduce bacterial adherence to sutures and to decrease microbial viability both in vitro and in animal models with a high safety profile. However, the majority of evidence comes

from case series and trials in other surgical specialties. Hence, the aim of this study was to investigate whether triclosan coated sutures will reduce wound healing complications in hip and knee arthroplasty surgery.

b) A meta-analysis of tranexamic acid effect on wound healing complications and infections after primary total hip arthroplasty has been conducted. The role of tranexamic acid in reducing blood loss and allogeneic blood transfusions has been previously investigated. However, taking into account that allogeneic blood transfusions have been linked to an increased rate of wound and systemic infections, I conducted this meta-analysis with the aim of investigating whether tranexamic acid will reduce wound healing complications including infections after primary hip arthroplasties which has not been previously studied.

c) Late periprosthetic infections invariably lead to implant removal with a two stage revision strategy being the treatment of choice in most centres whereas early infections and acute haematogenous infections may be managed with implants retention and serial debridements. Accordingly, I have conducted the following studies to investigate the efficacy of strict strategies and novel approaches implemented over the last 10 years at University College London Hospital in treating PJIs:

    1) Is Single-stage Revision According to a Strict Protocol Effective in Treatment of Chronic Total Knee Arthroplasty Infections? The aim was to determine infection control rates associated with the single-stage approach when applied in a highly selected group of patients and compare them with results of the two-stage procedure.
    2) Periprosthetic Joint Infections after Total Hip Arthroplasty: The Ten Year Outcomes of an Algorithmic Approach. The aim was to present the strategy applied for treatment of various subgroups of periprosthetic joint infection at a centre of excellence and report the outcome of infection rates.

Results

Contrary to the evidence from other surgical specialties that triclosan coated sutures are effective in preventing periprosthetic joint infections, no such effect was seen in the randomised controlled trial conducted. In fact, triclosan coated sutures were associated with higher rates of wound complications (P=0.03).

Tranexamic acid on the other hand, led to a 3% reduction in the risk of developing wound complications including infections compared to the control group (Risk difference -0.03, 95%, confidence interval CI -0.05 to -0.01, P-value 0.01). This protective effect of tranexamic acid against infections has not been previously reported in the literature.

In a highly selected population, none of the 28 patients who underwent a single stage revision developed recurrence of infection whereas five out of 74 patients (7%) in the two-stage revision group developed reinfection. The results of single-stage revision in this retrospective study reflect the strict inclusion criteria, surgical technique and multi-disciplinary approach which were associated with high rates of eradicating infection. However, randomised controlled trials are necessary to confirm those results in comparison to other treatment modalities.

The use of a strict strategy driven by an experienced multi-disciplinary team working simultaneously at a centre where infection is being dealt with on a regular basis has resulted in high rates of infection-free survival with 188 out of 204 patients (92%) achieving successful eradication of their infections and returning to their expected functional level with no evidence of recurrence or loosening, wearing away, or malpositioning on follow-up radiographs. This compares well with evidence from the literature confirming that centres of excellence only can achieve as high infection eradication rates as reported in this study.

Conclusion

The results of the included studies suggest using tranexamic acid but not triclosan coated sutures in routine primary hip and knee arthroplasty surgery to reduce wound healing complications and infection. Treating periprosthetic joint infections requires a multi-disciplinary team approach working at a tertiary centre dealing with infections on a regular basis. Single-stage revision in acute and chronic joint infections is appealing and gaining the momentum but randomised controlled trials are necessary to confirm its efficacy against other treatment modalities.

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Abbreviations

Order	Abbreviation	Meaning
A	AAOS	American Academy of Orthopaedic Surgeons
	AE	Adverse event
	ALC	Antibiotic loaded cement
	AR	Adverse reaction
	ASA	American Society of Anaesthesiologists grading system
C	CDC	Center for Disease Control
	CI	Confidence interval
	CRP	C-reactive protein
	CT	Computed tomography
D	DVT	Deep vein thrombosis
E	EACA	Epsilon aminocaproic acid
	ESR	Erythrocyte sedimentation rate
I	IDSA	The Infectious Diseases Society of America
	IL6	Interleukin-6
	ISRCTN	International Standard Randomised Controlled Trial Number
		Leucocyte esterase
L	LE	Low molecular weight heparin
	LMWH	
		Metal artefact reduction sequence
M	MARS	Medicines and Healthcare products Regulatory Agency
	MHRA	Minimal inhibitory concentration
	MIC	Magnetic resonance imaging
	MRI	Methicillin Resistant Staphylococcus Aureus
	MRSA	Methicillin Resistant Staphylococcus Epidermidis
	MRSE	The Musculoskeletal Infection Society
	MSIS	
		National Health Service
N	NHS	National Institute of Clinical Excellence
	NICE	
		Pulmonary embolism
P	PE	Periprosthetic joint infection
	PJI	Polymethylmethacrylate
	PMMA	Polymorphonuclear
	PMN	Prosthesis of antibiotic loaded acrylic cement
	PROSTALAC	
		Quality assessment score
Q	QAS	
		Randomised controlled trial
R	RCT	Risk difference
	RD	Regional Ethics Committee

	REC	Research and Development
	R&D	
		Serious adverse event
S	SAE	Serious adverse reaction
	SAR	Scottish intercollegiate guidelines network
	SIGN	Summary of Product Characteristics
	SmPC	Société de Pathologie Infectieuse de Langue Française
	SPILF	Suspected serious adverse reaction
	SSAR	Surgical site infections
	SSI	Suspected unexpected serious adverse reaction
	SUSAR	
		Total hip arthroplasty
T	THA	Total hip arthroplasty
	TJA	Total knee arthroplasty
	TKA	Tumour necrosis factor
	TNF	Tranexamic acid
	TXA	
		University College London
U	UCL	University College London Hospital
	UCLH	Ultrasound
	US	
		Vicryl Plus sutures
V	VPS	
		White blood cell count
W	WBC	

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Chapter 1

Management of Periprosthetic Joint Infections: The Current Literature

1.1 Introduction

Periprosthetic infection in total hip (THA) and knee arthroplasty (TKA) was one of the most common and dangerous complications in the early years of joint replacement with a rate as high as 9.5% reported by Charnley. More recently, the incidence has decreased significantly as a result of improvements in operating room discipline, surgical technique, more assiduous preoperative assessment of the patient, and the prophylactic administration of antimicrobial agents (Kaltsas, 2004). Although rates now are around one to two percent of all primary total joint arthroplasty (TJA) and five percent of arthroplasty revisions (Vanhegan et al., 2012b), the management from both the patient and surgeon perspective is challenging, often requires a prolonged course of treatment, is associated with a considerably increasing cost to the healthcare system estimated at four times the cost of a primary TJA without infection (Dreghorn and Hamblen, 1989), and may lead to complications such as recurrence of infection and septic loosening of the prosthesis (Burnett et al., 2007).

Multiple risk factors for developing infection after TJA have been identified including length of the procedure, the number of previous operative interventions, rheumatoid arthritis, diabetes mellitus, excess alcohol intake, chronic lung and liver disease, sickle cell disease, obesity, poor nutrition, and immunosuppressive medications including systemic steroids, any history of osteomyelitis or septic arthritis and presence of open skin lesions on the affected extremity (Luessenhop et al., 1996, Poultsides et al., 2013, Maoz et al., 2015, Bohl et al., 2016).

Infection following TJA can present a diagnostic challenge as there is no gold standard for determining whether an infection is present or not (Della Valle et al., 2011). The treatment of the infected TJA leads to a long difficult course for the patient, and frequently results in a suboptimal functional outcome. Various treatment modalities are available depending on a number of factors including, the acuteness or chronicity of the infection; the infecting

organism, its sensitivity profile to antibiotics, and its ability to manufacture glycolyx; the health of the patient; the fixation of the prosthesis; the available bone stock; and the particular philosophy and training of the surgeon (Haddad et al., 1999). Infected TJA should be approached with careful preoperative assessment and a well defined treatment plan as will be outlined in this review of the current standards of managing periprosthetic joint infections (PJIs) after THA and TKA.

1.2 Microbiologic Considerations

Although infection after TJA may be caused by haematogenous seeding, bacteria from the skin flora of the patient and airborne bacteria from theatre personnel may enter the wound at the time of surgery as well. Many studies have demonstrated that individuals moving around the operating theatre contribute the largest proportion of pathogenic bacteria to the wound. As a result, various measures have been introduced to control the operating environment including the use of laminar air flow and Charnley's ultraclean air system comprising sterile hoods and a body-exhaust system as well as prophylactic antibiotics, which have reduced rates of infection from 9% to 1.3% (Charnley, 1972, Ha'eri and Wiley, 1980). Another important source of infection is a leaky wound postoperatively and hence the importance of careful handling of the soft tissues and achieving a water tight seal at the time of wound closure. A good understanding of potential pathogens contaminating surgical wounds is essential in order to use the appropriate antibiotics for prophylaxis and treatment of infections. In most reports of PJIs, *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most common infecting organisms accounting for approximately 85%-90% of the infections (Barberan, 2006, Ribeiro et al., 2012). Some common but less frequent organisms include *Streptococcus* species and Gram negatives such as *Pseudomonas, Klebsiella, and Escherichia coli* which are usually secondary invaders of open, draining wounds in patients with deep sepsis of a TJA. Anaerobic microorganisms are isolated in 10% of such patients

(Vogelyl et al., 1996). Occasionally, the treatment of the infected arthroplasty is complicated by polymicrobial infections with particularly virulent organisms such as *Group D Streptococci, Pseudomonas*, fungal or mycobacterial infections which can cause a real challenge for the surgeon both to diagnosis and treat due to recurrent sepsis (Tian et al., 2014, Peel et al., 2012). Resistance of microorganisms such as *Staphylococcus aureus* and *Staphylococcus epidermidis* has been attributed in many reports to the ability of the organism to produce a slime layer, or a biofilm of glycocalyx. This layer is made up of a variety of polysaccharides synthesised by the bacteria as well as a range of host molecules which enables the organism to adhere to and survive on synthetic surfaces. *Staphylococcus epidermidis* is a usual cause of biofilm formation. Bacteria that exist within a biofilm are at least 500 times more resistant to antibiotics than bacteria which exist as individual free-floating cells (Trampuz et al., 2003). On the other hand, Methicillin-resistant strains cause 4-5% of hip and knee replacement infections (Health Protection Agency, 2016) but the mechanism of resistance has been attributed to an acquired genetic determinant, mecA or mecC which encode for a low affinity penicillin binding protein that can continue the catalysis of peptidoglycan transpeptidation in the presence of high concentrations of beta-lactam antibiotics (Kim et al., 2013).

1.3 Classification of PJI

Classification systems are devised to help guide treatment and are primarily based on the onset of symptoms from the time of surgery and the route by which the infecting organism gains access to the joint space. Coventry (Coventry, 1975) classified infections after THA into three stages: acute infections which develop within three months of the surgery and are caused by contamination at the time of the operation (Stage I), delayed infections which are more indolent and may not become apparent until several months after the hip replacement and are also related to contamination at the time of surgery (Stage II) and haematogenous

infections which are associated with a previous infection remote to the hip joint such as a respiratory, dental and urinary tract infection and may develop soon after the remote infection or as late as two or even several years after the hip replacement (Stage III).

Tsukayama (Tsukayama et al., 1996) expanded the classification into four categories to facilitate further the management of these patients: 1) positive intraoperative cultures from revision TJA without other features of obvious infection where the infection should be treated with six weeks of intravenous antibiotics and no operative intervention; 2) early postoperative infections (occurring less than 1 month postoperatively) where treatment should include debridement, retention of the prosthesis, and intravenous antibiotics; 3) late chronic infections (occurring more than 1 month postoperatively with an insidious onset) which requires removal of the prosthesis and a staged revision; and 4) acute haematogenous infections where debridement is sufficient if the prosthesis is well fixed. However, if the prosthesis is loose, treatment should be the same as that for a late chronic infection.

1.4 Definition of PJI

Over time, various definitions of surgical site infections (SSIs) including PJIs have been devised (Parvizi, 2011, Osmon et al., 2013, Parvizi et al., 2011c, CDC, 2015, Parvizi and Gehrke, 2014) to provide a platform for communication and improve treatment outcomes. However, a number of challenges deemed it impossible to reach a universal definition due to the variability of the 1) infecting organisms and their virulence, 2) hosts immune response, 3) criteria used for defining infection including the time of onset (early vs. late), source of infection (postoperative vs. hematogenous) and tissues involved (superficial vs. deep) and 4) diagnostic tools utilised to establish a diagnosis (Oussedik et al., 2012, Sukeik and Haddad, 2009c). With so many variations of definitions, it has been internationally recognised that there is a need for a universal definition in order to compare practice and drive research and

to determine the optimum strategies for prevention and management of PJIs. Some of the more common definitions and classification systems for SSIs/PJIs are detailed in Table 1.1 (Parvizi, 2011, Parvizi and Gehrke, 2014, CDC, 2015, Oussedik et al., 2012, Wilson et al., 1986, Parvizi, 2010, Osmon et al., 2013).

The National Institute of Clinical Excellence (NICE, 2003) in the United Kingdom provides guidelines on the management of wound infections and bases its definition of an SSI on that agreed by the Center for Disease Control (CDC). NICE also recognises the ASEPSIS wound scoring system which was devised by Professor Wilson at University College London Hospital in 1986 (Wilson et al., 1986, Wilson et al., 1990) for postoperative surveillance of wound healing and effectiveness of antibiotic treatment after infections. ASEPSIS provides the advantage of a very detailed assessment of the surgical wound but can be quite time consuming to fill out on day to day clinical assessment. (Table 1.1)

The Société de Pathologie Infectieuse de Langue Française (SPILF) organised a consensus meeting with other French speaking recognised bodies including the French Society of Orthopaedics and Trauma Surgery and The French Society of Anesthesiology and Intensive Care. A definition of PJI was agreed and this provided a platform for communication of clinical practice and research within the French speaking world (SPILF, 2010). (Table 1.1)

In 2010, The American Academy of Orthopaedic Surgeons (AAOS) developed guidelines and an evidence report on the management of PJI (Parvizi, 2010). The working party involved in developing these guidelines included members of the CDC and experts in the field. The guidelines described two categories: high and low probability of PJI depending on risk factors and clinical and radiological evidence. An algorithm for clinical tests was provided but without specific cut off values for these tests. (Table 1.1)

Following that, The Infectious Diseases Society of America (IDSA) described the presence of a sinus tract in communication with the joint as a definitive criterion and histopathological findings when present as highly suggestive of infection. They also described the work up required prior to this including a history with a particular reference to pain and investigations including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), arthrocentesis and blood cultures. However, specific values suggesting the relevance of these results were not provided. (Table 1.1)

Almost simultaneously with the IDSA, The Musculoskeletal Infection Society (MSIS) convened to establish a definition of PJI to be used by recognised bodies including the CDC as a gold standard for communication. This definition includes major and minor criteria that can easily be measured and members of the CDC were also on the panel (Parvizi et al., 2011b). (Table 1.1)

Professors Thorsten Gehrke and Javad Parvizi recognised that the longstanding issue with the prevention and treatment of PJIs was that although much research into the topic had been undertaken, there was a failure to answer fundamental questions about the subject due to lack of high level evidence. Therefore, they organised the International Consensus Meeting on PJI in Philadelphia in 2013 with the aim of answering some of these important questions. An outcome of this meeting was the creation of a definition for PJI, constituting 2 major and 5 minor criteria. This definition was formulated on the basis of existing evidence and a consensus of expert opinions. The presence of at least 1 major criterion or 3 minor criteria is required for a diagnosis of PJI. This includes analyses of tissue and aspirate cultures, laboratory tests such as ESR, CRP, polymorphonuclear (PMN) percentage, and synovial fluid white cell count (WBC) and neutrophil count on microscopy. The same definition was then adopted by the CDC with clarification of the definition of matching organisms and appropriate tissue sampling. CDC also stated that the laboratory cutoffs quoted in this

definition should not guide clinicians in the actual clinical diagnosis of infection but instead, they should refer to the MSIS consensus definition for clinical use (CDC, 2015). (Table 1.1)

1 **Table 1.1** A summary of common surgical site and periprosthetic joint infection definitions

Study	**Definition**	**+ve**	**-ve**
ASEPSIS (Wilson et al., 1986)	A scoring method for post operative wound infections for use in clinical trials A score of 1 to 5 is given for each of the following parameters dependent on the proportion of wound affected: -serous exudate -erythema -purulent exudate -separation of deep tissues Additional points are then given for: -antibiotic use -drainage of pus under local anaesthetic -debridement of wound under general anesthetic -serous discharge -erythema -purulent exudate -separation of deep tissues -isolation of bacteria -inpatient stay more than 14 days	Recognised by NICE as a valid measure for assessment of surgical site infection	Score is time consuming to carry out in daily clinical practice

	Score **Meaning** 0 to10 No infection Normal healing 11 to 20 Disturbance of healing 21 to 30 Minor infection 31 to 40 Moderate infection ≥ 41 Severe infection		
(SPILF, 2010)	Classification according to aetiology, location and duration Diagnosis: Presence of a fistula close to the prosthesis confirms infection until proven otherwise Post operative signs suggestive of infection: - unusually strong pain or its recurrence after a symptom free period - purulent discharge from a surgical wound - disunion, necrosis or scar inflammation - general signs of fever - radiological appearance of loosening Biological signs: WBC is not a good positive or negative predictor of infection Normal ESR and CRP do not exclude infection CRP should be used for monitoring of infection Suspect infection with ESR >30mm and CRP >13.5mg/l	Includes physical signs Provides biological parameters Describes imaging techniques for diagnosis	Specificity and sensitivity of biological parameters not given High level of clinical suspicion may lead to over diagnosis of PJI

	Imaging modalities: CT, MRI, US and nuclear medicine imaging suggestive of infection		
AAOS (Parvizi, 2010)	High probability of infection: One or more symptom AND at least one or more of the following: Risk factors (supported by evidence or expert opinion), physical exam findings (e.g. warmth, effusion, redness, swelling or a sinus tract associated with the joint) or radiological evidence of implant loosening/osteolysis Low probability of infection: Pain or joint stiffness only and no risk factors, physical examination findings or radiological evidence of implant loosening /osteolysis Algorithm provided for clinical tests: If ESR and CRP raised joint aspiration is recommended If joint aspiration provides positive differential cell count and positive culture – infection is likely If only one of the above is positive repeat aspiration and if positive infection is likely If second aspiration is negative and surgery is planned frozen section is recommended	Applicable to hip and knee surgery only Risk factors included Physical signs included Useful algorithm	Amount of samples for aspirate/culture may miss diagnosing some PJIs
IDSA (Osmon et al., 2013)	Definite: 1) Sinus tract communicating with the prosthesis 2) There is purulence around the prosthesis without any other known cause Highly suggestive: 1) Acute inflammation on histopathologic examination of periprosthetic tissue at the time of surgical debridement OR prosthesis removed is highly suggestive of PJI as defined by the attending pathologist 2) ≥2 Intra-operative cultures yielding same organism, OR combined aspiration and culture 3) Cultures grow a virulent microorganism from tissue or synovial fluid samples	Clear information stipulates that at least 3 or optimally 5 periprosthetic samples OR explanted prosthesis should be submitted for anaerobic and aerobic cultures Antibiotics should be	In the absence of a skilled pathologist PJI may be missed

	Additional information - PJI can be present if the given criteria are not met. All available information should be taken into account when diagnosing PJI - Intra-operative diagnosis is reliable when interpreted by a skilled pathologist	withheld for 2 weeks prior to cultures being taken if possible	
MSIS (Parvizi et al., 2011b)	Major criteria: 1) there is a sinus tract communicating with the prosthesis; or 2) a pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint; or Minor criteria: 3) when 4 of the following 6 criteria exist: a. elevated ESR and CRP b. elevated synovial WBC c. elevated synovial PMN percentage d. presence of purulence in the affected joint e. isolation of a microorganism in one culture of periprosthetic tissue or fluid, or f. greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification **Additional Information** Please note that a PJI may be present if less than 4 of these criteria are met		
International consensus group (Gehrke and	Major criteria: 1) A sinus tract communicating with the joint; or 2) 2 positive phenotypically identical organisms on cultures taken in periprosthetic sampling; or	Accompanying declaration states infection may be present when these	

Parvizi, 2014)	Minor Criteria: 3) when 3 of the following 5 criteria exist: a. elevated ESR & CRP b. elevated synovial fluid WCC OR ++ change on leucocyte esterase test strip c. elevated synovial fluid PMN% d. a single positive culture e. positive histological analysis of periprosthetic tissue	criteria are not met Further stipulation of values of the minor criteria is given according to acuteness or chronicity of infection	
(CDC, 2015)	Major Criteria: 1) A sinus tract communicating with the joint; or 2) 2 positive periprosthetic tissue or fluid cultures with matching organisms; or Minor Criteria: 3) when 3 of the following 5 criteria exist: a. CRP >100mg/L AND ESR >30mm/hr b. synovial fluid WCC >10,000 cells/μL OR ++ change on leucocyte esterase strip test of synovial fluid c. elevated synovial fluid PMN percentage (>90%) d. a single positive periprosthetic tissue or fluid culture e. positive histological analysis of periprosthetic tissue (more than 5 PMNs per high power field) Additional Information Further details given about: 1) definition of matching organism 2) positive cultures of hardware from a hip or knee can be used to meet criterion 2 3) definition of sinus given	Specific for hip and knee replacement only	

1.5 Prevention of PJIs

1.5.1 Antibiotic Prophylaxis

Prophylactic antibiotics are defined as those given before, during or after surgery to prevent infection. Current UK practice suggests that prophylactic antimicrobial agents should cover expected pathogens, take into account local resistance patterns and have a narrow spectrum whilst considering cost (SIGN, 2014). The role of antimicrobial prophylaxis has been established to be the single most significant factor in the prevention of deep wound infection following TJA (Hanssen and Osmon, 1994). Meehan (Meehan et al., 2009) investigated the optimal time for prophylactic antibiotic administration in an animal model and reported that bactericidal action was most effective when antibiotics were present within tissues prior to surgery. Current guidance obtained from consensus between the CDC and AAOS recommends administration of prophylactic antibiotics an hour prior to incision and continuing antibiotics for 24 hours postoperatively (Illingworth et al., 2013). However, NICE and SIGN guidelines suggest a single dose except in special circumstances such as prolonged surgery or major blood loss (SIGN, 2014). Cephalosporins including cefuroxime and cefazolin are the most commonly prescribed prophylactic antibiotics as per AAOS recommendation due to broad spectrum coverage against penicillinase producing methicillin susceptible Gram positive *Staphylococci and Streptococci*. Alternatives for allergic patients include clindamycin, teicoplanin and vancomycin (Osmon et al., 2013). There are numerous benefits to using cephalosporins as they cover most organisms encountered in orthopaedic surgery. Furthermore they have a proven evidence base, good safety profile and are inexpensive. In the UK, there has been a trend though towards avoiding cephalosporins due to the high rates of associated *Clostridium difficile* infections (Aujla et al., 2013). Al-Maiyah (Al-Maiyah et al., 2005) reported an increased resistance of coagulase (-) *Staphylococci* to

cephalosporins and recommended a revised prophylaxis strategy avoiding cephalosporins. However, it is worth noting that their conclusion may be related to the extensive usage of cephalosporins as a first line drug for prophylaxis in joint replacement surgery. Furthermore, a recent review examining the potential association of *Clostridium difficile* infections with cephalosporins showed no clear association between overall cephalosporin prescribing (or the use of any particular cephalosporin) and *Clostridium difficile* incidence. Hence, other factors should be assessed rather than focusing on the exclusion of individual drug classes (Wilcox et al., 2017). AlBuhairan (AlBuhairan et al., 2008) showed in a systematic review of antibiotic prophylaxis in joint arthroplasty that there is no evidence that any type of antibiotic prophylaxis has better results than any others and that selection should be on the basis of cost and local availability. Cranny (Cranny et al., 2008) reported that there is insufficient evidence to determine whether there is a threshold prevalence of *Methicillin Resistant Staphylococcus aureus* (MRSA) at which switching from non-glycopeptide to glycopeptide antibiotic prophylaxis might be clinically effective and cost-effective. Furthermore, the AAOS suggests routine antibiotic prophylaxis for 2 years following THA prior to various procedures associated with significant risk of bacteraemia such as dental cleaning and extraction (Parvizi and Della Valle, 2010).

The prophylactic role of antibiotic loaded cement (ALC) in primary TJA has also been assessed in prospective studies in over 1600 cases. In data from the Scandinavian arthroplasty registers, with an exhaustive follow-up of more than 240000 hip replacements, infection rate was reduced by 50%. Human pharmacokinetics during THA showed antibiotic concentrations 20 times the minimal inhibitory concentration (MIC) in drainage fluids. No toxic concentrations have been detected in blood or urine, and no allergies, toxic effects, mechanical failures or selection of resistant microorganisms have been observed. Therefore, ALC prophylaxis is now widely used in countries with prostheses registers. Antibiotics leach

from Palacos bone cement in higher concentrations and for longer periods than from Simplex-P, CMW, and Sulfix acrylic bone cements (Penner et al., 1999). Furthermore, Palacos with gentamicin is more resistant to fracture than Zimmer or Simplex-P cement mixed with gentamicin (Callaghan et al., 1985). The most commonly used antibiotics in ALC include tobramycin, gentamicin and vancomycin (Scott and Higham, 2003). The combination of vancomycin and one of the aminoglycosides provides a broad spectrum of coverage for organisms commonly encountered with deep periprosthetic infections. The presence of tobramycin has a synergistic like effect on the bactericidal activity of vancomycin. A low dose of ALC not exceeding 10% of the cement weight should be used for prophylaxis. However, when used in treatment of infected THA, ALC is used in higher doses as an adjuvant to excision of infected and devascularised tissues and systemic antibiotic treatment (Langlais et al., 2006).

Antimicrobial coated sutures have also been widely used to prevent microbial colonisation of suture material in operative wounds (Barbolt, 2002). For example, the coated Vicryl Plus triclosan (polyglactin 910) suture was developed and approved by the Food and Drug Administration (FDA) in 2002. Triclosan is a broad-spectrum antiseptic which has been widely used in humans for more than 30 years (Barbolt, 2002) and is effective against *Staphylococcus aureus* and *Staphylococcus epidermidis* including methicillin-resistant strains, vancomycin-resistant *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Escherichia coli* (Edmiston et al., 2006, Rothenburger et al., 2002). Vicryl Plus sutures (VPS) have recently been shown to reduce bacterial adherence to sutures and to decrease microbial viability both in vitro and in animal models (Edmiston et al., 2006, Gomez-Alonso et al., 2007, Rothenburger et al., 2002, Storch et al., 2002a, Storch et al., 2002b) with a high safety margin, little or no risk of allergic reactions and no evidence of microbial resistance (Barbolt, 2002, Gilbert and McBain, 2002). However, the majority of evidence is related to studies in

general surgery and no trials to date have been published in Orthopaedics and lower limb arthroplasty.

1.5.2 Blood Management

Numerous studies have shown that allogeneic blood transfusion increases the risk of SSI through the mechanism of immunomodulation (Bloch et al., 2013). Moreover, rates of SSI and lower and upper respiratory tract infections were increased after elective TJA in patients receiving allogeneic blood transfusion compared with patients who did not receive blood transfusion (Friedman et al., 2014). On the other hand, the role of autologous transfusion in the risk of developing SSI and PJI remains inconclusive. Taken together, much effort should be exercised perioperatively to reduce the need for any type of blood product transfusion. A variety of blood-conserving techniques have been developed to decrease blood loss and postoperative transfusion rates including controlled hypotension, regional anaesthesia, intraoperative blood salvage, erythropoietin and antifibrinolytic agents such as tranexamic acid. However, the direct relationship between using these techniques and reducing wound complications and infections have not been adequately explored in the literature.

1.5.3 Other Measures

Other measures to prevent infection include stopping smoking and excessive alcohol consumption (Bradley et al., 2007, Moller et al., 2002, Singh, 2011), weight loss in the obese and control of comorbid diseases such as diabetes, sickle cell disease, liver and kidney dysfunction and rheumatoid arthritis (Marchant et al., 2009, Cohen et al., 2005, Shrader et al., 2006, Doran et al., 2002). Temporary cessation of medications such as methotrexate also decreases the risk (Bridges et al., 1991) although this needs to be balanced against the risk of a rheumatoid flare. In theatre, staff should be kept to a minimum (Malinzak and Ritter, 2006), appropriate use of gowns, face masks, double gloving, hand-washing, skin preparation and

temperature regulation should always be implemented and duration of surgery should be kept as short as possible. The use of pulsatile lavage has also been reported to remove up to 87% of all organisms from wounds (Hope et al., 1989). In the perioperative period, periodontal and urinary tract sepsis must be eradicated early to prevent haematogenous seeding of the prosthesis (Della Valle et al., 2004). Screening for *MRSA* and decolonisation of carriers have also been linked to a reduction in *MRSA* surgical wound infections and bacteraemia (Keshtgar et al., 2008).

1.6 Diagnosis of PJI

1.6.1 History and Physical Examination

A thorough history and physical examination are important to identify the type of PJI encountered and assess patient's risk factors and suitability for surgical treatment. Acute infection according to Tsukayama (Tsukayama et al., 1996) presents within 4 weeks of the index procedure and is characterised by continuous pain and an erythematous, swollen and fluctuant wound with purulent discharge and occasional wound dehiscence. Systemic symptoms such as fever and chills may also occur. Chronic infection on the other hand, occurs after 4 weeks from the index procedure (Tsukayama et al., 1996) and is characterised by gradual deterioration of function, persistent pain from the time of the operation and a draining sinus. Relevant history includes prolonged wound discharge and wound healing after multiple courses of antibiotics. A previous history of infection is also important especially in tuberculosis where reactivation of infection may occur after a prolonged period of quiescence. Haematogenous infection can occur at any time after the index operation (Tsukayama et al., 1996) and typically involves a prosthesis that has been functioning well for months or years. The most frequent primary seeding site is skin and soft tissue infections (Zimmerli and Moser, 2012). However, other sources of infection may include the urinary,

respiratory, and gastrointestinal tract, as well as recent dental work (Maderazo et al., 1988). This type of infection is more likely to occur in immunocompromised patients and hence the importance of carefully assessing this subset of patients for comorbidities such as diabetes, chronic renal impairment, inflammatory arthropathy and malignancies.

Early diagnosis of PJI in a well fixed implant may allow salvage of the prosthesis using an aggressive early debridement strategy with exchange of modular components whereas a delay in diagnosis or in the case of chronic infections, a single or staged exchange procedure may be more appropriate to eradicate the infection. In either case, rapid intervention based on thorough assessment has been deemed a primary prognostic factor for successful treatment of infection as it may prevent biofilm formation by the infecting bacteria (Moyad et al., 2008).

1.6.2 Serological Tests

The WBC and PMN percentage have been found to have a minimal role in routine workup of patients with suspected PJI due to low sensitivity and specificity (Toossi et al., 2012, Spangehl et al., 1999). However, the CRP and ESR should be used as a screening tool for all patients with suspected infection. The CRP level reaches maximum values within 48 hours from surgery and returns to normal within 3 weeks whereas ESR may remain elevated for months post surgery (Shih et al., 1987, Moyad et al., 2008). Therefore, an elevated CRP is more accurate in identifying infection (Haaker et al., 2004). A CRP level of > 10 mg/L and an ESR level of >30 mm/hr correlated with PJI in all THAs that were complicated by deep infection in two studies (Spangehl et al., 1999, Schinsky et al., 2008). As a result, authors recommended combining both tests to improve the accuracy of diagnosing infection. It is important though to recognise that ESR and CRP are nonspecific markers of inflammation and that they are frequently elevated in other inflammatory and infectious conditions as well as malignancy which may cause false positive results for PJI. Additionally, they are elevated

in the early postoperative period after a routine hip or knee replacement. Therefore, Bedair (Bedair et al., 2011) and Yi (Yi et al., 2014) defined the threshold values for CRP in acute postoperative PJIs of the hip and knee as 93 and 95mg/L respectively. Greidanus (Greidanus et al., 2007) suggested that both ESR (sensitivity, 0.93; specificity, 0.83; positive likelihood ratio, 5.81; accuracy, 0.86) and CRP (sensitivity, 0.91; specificity, 0.86; positive likelihood ratio, 6.89; accuracy, 0.88) have excellent diagnostic test performance. In a recent study of 320 PJIs, Zajonz (Zajonz et al., 2015) showed no differences between hip and knee arthroplasty patients regarding levels of inflammatory markers. Parvizi (Diaz-Ledezma et al., 2014) suggested in a recent study that the best diagnostic strategy after confirming abnormal CRP and ESR levels would be a diagnostic aspiration of the joint. On the other hand, the AAOS Clinical Practice Guidelines on PJIs (Parvizi and Della Valle, 2010) suggest that even normal levels of ESR and CRP do not rule out PJI, and that these tests alone should not be relied on for definite exclusion of PJI.

Serum Interleukin-6 (IL-6) and procalcitonin have also been investigated and were initially presented as valuable markers for detecting PJIs (Berbari et al., 2010, Di Cesare et al., 2005, Shaikh et al., 2015). However, recent studies showed no superiority of either test over CRP in diagnosing infection (Glehr et al., 2013, Drago et al., 2011, Yuan et al., 2015). Additionally, studies relating to IL6 have been criticised for not accounting for the confounding influence of previous antibiotic use and associated inflammatory conditions on IL6 performance (Berbari et al., 2010, Di Cesare et al., 2005).

Other serum biomarkers elevated in PJI which are under investigation for future application include tumour necrosis factor (TNF)-α, short-chain exocellular lipoteichoic acid, soluble intercellular adhesion molecule-1, and monocyte chemoattractant protein-1 (Chen et al., 2014).

1.6.3 Synovial Fluid Tests

Hip and knee aspirations are performed using the surgeon's preferred technique. However, a strict aseptic approach is essential to reduce false positive results and prevent iatrogenic periprosthetic infection. Fluoroscopic guidance is usually utilised for the hip joint but ultrasound guided hip aspirations have also been reported (Battaglia et al., 2011). Local anaesthetic and contrast material should be avoided due to the potential bactericidal effect and associated false negative results (Ali et al., 2006, Schmidt and Rosenkranz, 1970). Similarly, it is recommended that patients stop any antibiotics for a minimum of 2 weeks prior to obtaining synovial fluid or cultures to avoid false negative results (Della Valle et al., 2011). However, in case antibiotics are continued to avoid uncontrolled recurrence of the infection, it is also possible to analyse the synovial WBC and perform a PCR to investigate infection or use biomarkers such as α-Defensin which does not seem to be affected by continuation of antibiotics (Deirmengian et al., 2014). The synovial fluid should be sent for microbiologic cultures, WBC count and differentials. Blood culture flasks should be used for the synovial fluid (Font-Vizcarra et al., 2010), and specialised media are required for suspected atypical infections, such as Lowenstein-Jensen media for mycobacteria (Woods, 2002) or Sabouraud's dextrose agar for fungi (O'Shaughnessy et al., 2003). Prolonged culture incubation for 14 days may be required if *P. acnes*, fungi or mycobacterium are suspected (Schafer et al., 2008, Larsen et al., 2012). However, cultures for mycobacterium and fungi should not be done routinely as this would not be cost-effective (Tokarski et al., 2013). If the culture results are negative in the setting of elevated synovial and serum markers suggestive of infection, repeat aspiration should be performed prior to surgery or initiation of antimicrobial treatment (Barrack et al., 1997). The optimal cut-points of synovial WBC count, PMN percentage and serum CRP levels for diagnosing acute and chronic hip and knee PJIs are detailed in Table 1.2 (Bedair et al., 2011, Yi et al., 2014, Parvizi et al., 2011b).

Table 1.2 Laboratory Threshold Values for Periprosthetic Joint Infection of the Knee and Hip

	Acute		Chronic	
	TKA	**THA**	**TKA**	**THA**
Serum CRP (mg/L)	95	93	10	10
Synovial WBC Count (cells/µL)	27,800	12,800	1100 to 4000	3,000
Synovial PMN Cells (%)	89	89	64 to 69	80

TKA = total knee arthroplasty; THA = total hip arthroplasty; CRP = C-reactive protein; WBC = White blood cell; PMN = polymorphonuclear

Leucocyte esterase (LE) testing is reported to be cheap, easily applicable with high sensitivity (80%) and specificity (100%) rates (Parvizi et al., 2011a). However, it is important to remember that the presence of blood in the synovial fluid aspirates, may negatively affect the interpretation of the LE strip but that centrifuging the sample overcomes this problem without affecting the accuracy of the test (Aggarwal et al., 2013, Wetters et al., 2012).

Synovial CRP and IL-6 have also been proposed to improve diagnostic accuracy in PJI. For example, combined measurement of synovial CRP and α-Defensin levels demonstrated a sensitivity of 97% and a specificity of 100% for the diagnosis of PJI and correctly diagnosed 99% of cases as aseptic or infected (Deirmengian et al., 2014). However, despite some studies suggesting a superiority of synovial CRP over serum CRP (Parvizi et al., 2012, Jacovides et al., 2011), a recent report suggested that synovial CRP does not offer a diagnostic advantage in detection of PJIs (Tetreault et al., 2014). Randau (Randau et al.,

2014) suggested that synovial IL-6 is a more accurate marker than serum WBC and CRP for the detection of PJIs and that combining serum and synovial IL-6, compared with performing each test individually improves the diagnostic yield. Recent studies have also shown that synovial IL-6 has high specificity and accuracy even when patients who were taking antibiotics and those with systemic inflammatory diseases were included (Deirmengian et al., 2010, Jacovides et al., 2011).

Other synovial biomarkers elevated in PJI which are under investigation for future application include cytokines such as IL-1β, IL-6, IL-8, IL-17, TNF-α, interferon-δ, and vascular endothelial growth factor, human β-defensin-2 (HBD-2) and HBD-3, and cathelicidin LL-37 (Chen et al., 2014). New technologies based on synovial fluid biomarker analysis, biofilm targeting and the application of metabolomics are currently underway. This includes biofilm visualisation and sequencing-based biomolecular methods, PCR-based electron spray ionization time-of-flight mass spectrometry (ESI-TOF-MS) and matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bizzini et al., 2010, Jacovides et al., 2012).

1.6.4 Imaging Modalities

Plain radiographs should be included in any workup for infected joint replacements. However, they are neither sensitive nor specific for detection of infection. Radiographic findings including loosening and osteolysis are common to both septic and aseptic failures. On the other hand, periosteal new bone formation and endosteal scalloping, are more suggestive of infection but are not seen in all cases (Spangehl et al., 1999).

Computed tomography (CT) provides detailed analysis of bony structures and may show evidence of soft tissue collections. However, it is limited due to metal artefact, is associated with low sensitivity for detecting PJI and exposes patients to high doses of radiation

alongside the significant cost associated with using them (Cyteval et al., 2002). Magnetic resonance imaging (MRI) is also limited due to metal artefact and studies relating to accuracy of metal artefact reduction sequence (MARS) MRIs are limited in the literature (Talbot and Weinberg, 2015).

Scintigraphy studies may be helpful when results of serologic tests are falsely elevated due to inflammatory conditions and cultures of synovial fluid are unreliable because of administration of antibiotics or in the case of a dry tap especially if the patient is not planned for surgery (Enayatollahi and Parvizi, 2015). However, the cost of a scan is significant and comparable to that of a CT or MRI scan, the amount of radiation is equivalent to a CT scan, and results can remain positive for as long as one year after a knee or hip arthroplasty due to the increased uptake from the surgery itself. A number of isotopes including Technetium-99m, Gallium-67 citrate, and Indium-111-labelled WBCs have been used with variable sensitivities and specificities in detecting PJIs. Ouyang (Ouyang et al., 2014) reported in a recent systematic review that overall sensitivity and specificity for using triple phase bone scans to detect PJI was 0.83 and specificity was 0.73. However, the sensitivity and specificity for detecting infected arthroplasty of the hip (0.81 and 0.78, respectively) were significantly higher than those of the knee (0.75 and 0.55, respectively; $p < 0.05$). A meta-analysis of antigranulocyte scintigraphy with monoclonal antibodies studying PJI in THAs showed sensitivity and specificity of 83% and 80%, respectively (Pakos et al., 2007). On the other hand, sensitivity of Indium-111-labelled WBC labelled scans for detecting periprosthetic hip infections has been reported as low as 50% in the literature (Pill et al., 2006).

Fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) has been investigated over the last decade for a role in diagnosing PJIs. The investigation relies on the fact that inflammatory cells express more glucose transporters, resulting in intracellular accumulation

of deoxyglucose which cannot be metabolised by the cell and can be identified by PET imaging. Although a meta-analysis conducted in 2006 by Prandini et al (Prandini et al., 2006) reported a sensitivity of 94.1 % and a specificity of 87.3% for detecting PJI, another meta-analysis in 2008 (Kwee et al., 2008) reported the overall diagnostic performance of FDG-PET as moderate to high and warned about heterogeneity of studies available in the literature. Two further studies published over the last 3 years (Brammen et al., 2015, Gemmel et al., 2012) suggested that the role of FDG-PET in diagnosing PJI is still to be determined. It is worth noting as well that this type of imaging is currently only available in tertiary referral centres and that it costs three times the cost of a bone scan or MRI (Hsu and Hearty, 2012).

1.6.5 Intraoperative Assessment

Intraoperative assessment at the time of revision surgery starts with evaluating the tissue appearance and classically performing gram stains of fluid or tissue samples collected. However, it is important to recognise that neither tissue appearance nor gram staining are reliable indicators for ruling in or ruling out infection (Della Valle et al., 2004, Spangehl et al., 1999).

Intraoperative frozen sections have been reported as useful methods for detecting PJI in patients planned for revision surgery when other tests have been suggestive but not conclusive of infection (Enayatollahi and Parvizi, 2015). Samples from deep tissues including the interfaces between bone and cement and cement and the implant should be sent for analysis. An experienced pathologist is essential to interpret the results according to the number of WBCs visualised per high power field. A study of 175 revision arthroplasties recommended using 10 WBCs/high power field as a threshold for diagnosing infection with a sensitivity of 0.84 and specificity of 0.99 (Lonner et al., 1996). MSIS/CDC guidelines recognise more than 5 PMNs per high power field as a minor diagnostic criterion for PJI

(Parvizi et al., 2011b). A recent study suggested that at the time of second-stage reimplantation surgery, frozen section is useful in ruling in infection, where the specificity is 94%; however, there is less utility in ruling out infection, because sensitivity is only 50% (George et al., 2015). Intraoperative synovial fluid sampling follows the same principles as preoperative synovial fluid sampling as outlined previously.

Intraoperative cultures are presumed to be the gold standard for identifying PJI. However, they are subject to false-negative and false-positive results (Tsukayama et al., 1996). As with joint aspiration, careful technique and withholding antibiotics for at least 2 few weeks preoperatively are essential to reduce false negatives (Della Valle et al., 2011). The definitive diagnosis of PJI is made when the same organism is isolated from at least 2 intraopearive cultures (Parvizi et al., 2011b). However, various studies suggest that 3-6 samples are collected from superficial, deep and periprosthetic tissues in order to obtain an accurate diagnosis of infection (Atkins et al., 1998, Parvizi et al., 2009, Parvizi et al., 2011b). The explanted component should also be sent to the microbiology lab for sonication as this improves sensitivity of the cultures from 61-78% even with patients who are receiving antibiotic treatment (Trampuz et al., 2007). Furthermore, the use of sonication in combination with other diagnostic techniques, such as multiplex PCR, can improve the identification of bacteria compared with conventional methods (Portillo et al., 2012, Achermann et al., 2010). The incubation period for cultures should be at least 7 days. However, reports published recently suggest prolonging incubation for 14 days as this increases the chances of identifying organisms that otherwise may remain culture negative (26.4% additional cases were classified as infected at 14 vs. 7 days) (Schafer et al., 2008, Larsen et al., 1995).

In 10-15% of cases, despite the presence of clear signs for infection including gross purulence, cultures may still be negative (Parvizi et al., 2006). Possible causes may be

inappropriate collection of samples, short incubation duration and the use of antimicrobial therapy prior to samples collection. Interestingly though, Ghanem (Ghanem et al., 2007) demonstrated that the administration of preoperative antibiotics to patients with a positive preoperative joint aspirate did not interfere with the isolation of the infecting organism more than when antibiotics were stopped. Therefore, it is paramount to liaise carefully with microbiologists to facilitate rapid and accurate analysis of intraoperative samples. The identification of specific pathogens using PCR-based assays was originally investigated to improve identification of organisms that caused an infection. Earlier PCR-based assays however, led to a higher rate of false-positives due to contamination and higher false-negatives because the probes used could not cover the wide spectrum of pathogens responsible for infection. However, there are novel systems which aim to improve identification of organisms responsible for PJI such as the Ibis T5000 biosensor system which uses a pan-domain DNA-based amplification technique (Jacovides et al., 2012). In one study, Ibis T5000 was not only able to verify positive conventional culture results, but was also able to detect an organism in four out of five cases of PJI that was thought to be culture-negative. Additionally, Ibis found that 88% of the revision cases that were presumed aseptic were actually cases that had a subclinical infection (Jacovides et al., 2012).

1.7 Management of PJI

The goals of treatment are the eradication of infection and the restoration of function of the affected limb. Treatment options include: debridement with retention of components, single-stage revision, two-stage revision, multi-stage revision and long term suppressive antibiotics or salvage procedures in patients with high operative risk. The extent of infection and the interval for which it has been present play a role in the choice of the revision procedure and the chances for successful treatment following revision. Classifying infection into acute or

late infection aids in the treatment plan. Treatment of mycobacterial infections follows the same guidelines (Boeri et al., 2003).

1.7.1 Acute Infection

Debridement with component retention: Irrigation and debridement with or without exchange of mobile parts (femoral heads and acetabular inserts) and retention of the infected implant has been advocated for early or late infections with a short duration of symptoms, stable components, and overlying soft tissue and skin of good condition (Davis, 2005, Zimmerli et al., 2004). The aim of rapid intervention with thorough debridement is to prevent the production of any biofilm by the infecting organism which is paramount for a successful outcome (Crockarell et al., 1998). Difficulties with this approach include determination of the time of onset of infection and the establishment of a point beyond which it is no longer reasonable to retain the implant. Despite expeditious management with irrigation and debridement, acute TJAs may lead to recurrent infections. Success rates in the literature range between less than 10% and more than 60% (Crockarell et al., 1998, Deirmengian et al., 2003). Thus, patients should be advised that other options of treatment may be necessary in case of an unsuccessful attempt at retaining the prosthesis including a staged revision or salvage procedures.

1.7.2 Chronic Infection

In chronic infections, a successful outcome depends on several factors including the baseline health status of the patient, implant removal with a thorough debridement followed by culture specific antibiotic treatment postoperatively. During this period the laboratory and clinical signs of the infection must return back to normal. Reimplantation can either be performed at the same stage as the debridement as part of a single-stage procedure, or alternatively as part

of a two or multi-stage procedure where debridement and reimplantation are separated by a period of antibiotic delivery (Krbec et al., 2004, Mitchell et al., 2003).

1.7.2.1 Single-stage Revision

Advantages of simultaneous debridement and exchange of the prosthesis include the avoidance of additional surgical procedures in patients who have major medical problems, for whom the risks of additional procedures are cumulative. Success rates for eradication of infection with single-stage revisions ranged between 76-82% in most studies when antibiotic loaded cement has been utilised in comparison to only 58% without using it (Buchholz et al., 1981, Raut et al., 1995, Sanzen et al., 1988). However, Jackson (Jackson and Schmalzried, 2000) in a review of the literature reported that the indications for direct exchange are limited by several factors including: 1) Failures associated with (a) polymicrobial infection; (b) gram-negative organisms, especially *Pseudomonas* species; and (c) certain gram-positive organisms such as *Methicillin Resistant Staphylococcus epidermidis (MRSE)* and *Group D Streptococcus*, 2) Because single-stage revision requires that the implant be inserted with antibiotic loaded cement, patients with significant bone stock deficiency cannot be managed with this technique 3) Lack of data on the use of bone graft in association with single-stage revision 4) Difficulties with removal of a solidly fixed cemented prosthesis without destroying the remaining proximal femoral bone stock should the procedure fail to eradicate the infection. Nevertheless, single-stage revision remains a viable option which is associated with less morbidity and is less expensive than delayed exchange when used in carefully selected patients.

1.7.2.2 Two-stage Revision

Two-stage reimplantation is the gold standard for the treatment of infected joint arthroplasties today as the successful eradication of a TJA infection is over 90% (Lin et al., 2001).

Furthermore, it permits uncemented reconstruction and the use of allografts which is particularly important given the frequency of femoral and acetabular defects associated with THA infections (Berry et al., 1991, Haddad et al., 2000b, Lai et al., 1996). Alexeeff (Alexeeff et al., 1996) used massive structural allografts in the second stage of a two-stage procedure in 11 patients. They reported no additional sepsis at a mean follow-up of 4 years. The principles of a two-stage revision include removal of the implant along with all cement and necrotic tissue which contain infectious organisms, administration of systemic antibiotics postoperatively for 6 to 12 weeks and eventual implantation of a new prosthesis. A patient is deemed free of infection and able to proceed to second-stage arthroplasty when repeat joint aspirates after discontinuing antibiotics are negative, and blood parameters return to normal values. Placement of antibiotic loaded cement in the form of spacers during the intervening treatment period to deliver antibiotics locally has been popularised due to the even higher rates of eradicating infection achieving up to 95% in several studies (Hofmann et al., 2005, Younger et al., 1997). This system increases local antibiotic levels up to 200 times higher than those for systemic administration whilst preventing debris from accumulating in the potential joint space and soft-tissue contractures (Masri et al., 1998). When used in temporary spacers, antibiotic dosages up to 20 g per 40 g of bone cement have been reported without systemic side effects (Springer et al., 2004). For fungal infections, 100 to 150 mg of amphotericin B is typically added to the 40 g of bone cement in addition to other antibiotics chosen. However, when used for prophylaxis in single-stage revisions, a maximum dose of 2 grams per 40 grams mix is recommended to avoid weakening the mechanical properties of the cement. Such dose has shown a level of activity that passed for more than eighty days the level of minimum inhibitory concentration (MIC) of the most common pathogens (Stevens et al., 2005). It is also worth noting that the additive or synergistic effect of combining

antibiotics in the cement has been studied and showed improved efficacy and less resistance to the antibiotics used (Bertazzoni Minelli et al., 2004, Gonzalez Della Valle et al., 2001).

1.7.2.3 Spacers

Spacers are classified as static or non-articulating spacers, medullary dowels, and articulating or mobile spacers. Although antibiotic loaded cement beads have also been used previously, they are rarely advocated nowadays in the treatment of the infected joint arthroplasty due to the associated scarring and as a result, the difficulty in identifying and removing them at the second stage procedure (Taggart et al., 2002). Types of spacers include the following:

a) Static/nonarticulating spacers: Static or simple block spacers aim at maintaining the dead space and are mostly used in the acetabulum. They facilitate surgical dissection at the time of reimplantation and allow delivery of the antibiotics of choice according to sensitivities. Typically, 20 g of bone cement mixed with at least 2 or 3 g of powdered antibiotic provides an adequate volume for the acetabular defect. The disadvantage of a static spacer is that it does not allow physiological motion of the joint, although this has been associated with less generation of debris in comparison with mobile spacers (Burnett et al., 2007, Stockley et al., 2008)

b) Medullary dowels: A tapered cement dowel fashioned from the nozzle of a cement gun provides an excellent size and shape for a spacer to be inserted into the medullary canal during treatment of infected THA. A small bulb is left at the end of the dowel to prevent migration of the dowel down the femoral canal and help facilitate removal. Disadvantages include the potential for proximal femoral migration and the inability of using them in patients with severe femoral bone loss (Burnett et al., 2007, Stockley et al., 2008).

c) Mobile/articulating spacers (such as the PROSTALAC): The primary concept of this technique allows the patient to move the affected joint through a range of motion during

the time between prosthesis removal and insertion of the new prosthesis. The Prosthesis of Antibiotic Loaded Acrylic Cement (PROSTALAC) first developed by Duncan and Beauchamp (Duncan and Beauchamp, 1993) was composed of a metal femoral endoskeleton component covered with antibiotic loaded cement. The cement of the femoral head articulated with the bone of the acetabular bed, which could unfortunately lead to bone erosion and discomfort. An acetabular cement component was therefore introduced; preventing loss of acetabular bone, but the cement-on-cement articulation limited motion and caused discomfort. The PROSTALAC system now consists of a constrained cemented acetabular component with an articulating polyethylene liner and a femoral component with a modular head that is made intra-operatively with antibiotic loaded cement surrounding a stainless steel endoskeleton, using a series of molds. Whilst providing high doses of local antibiotic delivery, this system also allows earlier mobilisation out of bed and accelerated rehabilitation and discharge from the hospital between stages of treatment avoiding the complications associated with prolonged hospital stay and immobilisation (Haddad et al., 1999). More recently, the option to use a preformed PROSTALAC equivalent with fixed low-dose antibiotic content has become available. Prefabricated molds of different sizes are also now available, allowing the surgeon to select antibiotic dose and content. However, the disadvantages of preformed mobile spacers include limitation in implant sizes and antibiotic dose, often allowing delivery of only a single antibiotic. Mobile spacers formed in the operating room have the advantage of adjustable antibiotic dosing; a combination of antibiotics and the addition of an antifungal option as necessary. Disadvantages of mobile spacers formed in the operating room though include additional time to construct the implant, a limited number of sizes, additional cost, and complications may similarly occur.

Complications of spacers:

a) Implant and periprosthetic fractures: Surgeon made spacers in the operating room may be at higher risk for a fracture, especially with a mobile spacer, as a result of cement heterogeneity and inconsistencies in mixing. The use of higher antibiotic doses also leads to increased risk of fracture. A noncongruent femoral component fit on host femoral bone may lead to subsidence and fracture of the implant. Therefore, the surgeon should avoid impacting the mobile cement spacer during cementing which may predispose both the prosthesis and the bone stock deficient proximal femur to fracture (Burnett et al., 2007).

b) Antibiotic toxicity: A rare complication which may occur more frequently with surgeon constructed spacer implants when high doses of antibiotics are added to the cement (Masri et al., 1998). Patient factors which may potentiate antibiotic toxicity include renal failure. Therefore, renal function and antibiotic levels monitoring is crucial in this group of patients and should this complication occur, removal of the implant must be considered.

c) Instability: This occurs more frequently with knee spacers. However, in the hip, the use of a snap-fit polyethylene liner has reduced the incidence of this complication (Burnett et al., 2007).

Two-stage revision arthroplasty using antibiotic loaded cement but without a prolonged course of antibiotic therapy has also been reported by Stockley (Stockley et al., 2008) in a series of 114 patients for chronic THA infections. Infection was successfully eradicated in 100 patients (87.7%) at a mean follow-up of two years.

1.7.2.4 Multi-stage Revision

A three-stage reimplantation procedure is suitable for treatment of extensive bone defects in which the use of a large amount of morselised allograft can be anticipated. The bone bed created is allowed to incorporate for about 6 months and, in most cases, a cementless implant

is subsequently inserted (Landor et al., 2005). Multi-stage revision is also indicated when clinical presentation, blood parameters and cultures are suggestive of persistent infection requiring further debridement and possible repeat of PROSTALAC to eradicate infection after the first stage of revision.

1.7.3 Salvage Procedures

1.7.3.1 Long Term Suppressive Antibiotics

Chronic suppressive therapy for periprosthetic infections is indicated when an operation is refused by the patient or is believed to be associated with an unacceptable risk in medically unfit patients (Goulet et al., 1988). Infection is suppressed rather than eradicated with this type of treatment. The infecting organism must be identified and sensitive to the chosen antibiotic which should be effective orally and tolerable by the patient. Failures of treatment are due to the patient developing side effects like diarrhoea or recurrent candidiasis and the emergence of resistant strains.

1.7.3.2 Excision Arthroplasty

In life threatening or intractable hip or knee infections, an excision arthroplasty should be considered. Other indications for an excision arthroplasty include the elderly patient who is not capable of mobilising independently, those who are mentally impaired and may be unable to cooperate with the postoperative rehabilitation process, uncooperative patients such as intravenous drug abusers and the immunocompromised patients (Haddad et al., 1999). Excision arthroplasty is primarily aimed at pain relief and eradication of infection. However, such patients must be warned to expect at least 2-3cm of limb shortening and reliance upon a walking aid postoperatively (Sharma et al., 2005). The greater the bone loss, the more unsatisfactory an excision arthroplasty becomes.

1.7.3.3 Arthrodesis

Arthrodesis is an alternative treatment in PJI and has been described by Kostuik (Kostuik and Alexander, 1984) a series of 14 patients where the indications were young age, male gender and strenuous functional demands. Although all hips eventually fused and patients were able to mobilise independently, patients had an average of 4.6cm limb-length discrepancy.

1.7.3.4 Amputation

Amputation is rare and generally reserved for patients with life threatening infections, multiple unsuccessful revisions and vascular injuries.

Chapter 2

An RCT of Triclosan Coated versus Uncoated Sutures in Primary Hip and Knee Arthroplasty

2.1 Introduction

Total hip and total knee arthroplasties are among the commonest operations in orthopaedic practice. The thirteenth annual report of the National Joint Registry (NJR, 2016) showed that around 796,000 THAs and 870,000 TKAs were performed in England and Wales between 1 April 2003 and 31 December 2015.

Although infection after hip and knee arthroplasties may be caused by haematogenous seeding, it is more commonly due to bacteria entering the wound at the time of surgery (Sukeik and Haddad, October 2009). Various bacteria may contaminate not only the tissue in the surgical wound but the suture material (Uff et al., 1995, Rodeheaver et al., 1983). To prevent microbial colonisation of suture material in operative wounds, the coated Vicryl Plus triclosan (polyglactin 910) suture (Ethicon, Inc.) was developed and approved by the Food and Drug Administration in 2002. Triclosan is a broad-spectrum antiseptic which has been widely used in humans for more than 30 years (Barbolt, 2002) and is effective against *Staphylococcus aureus* and *Staphylococcus epidermidis* including methicillin-resistant strains, vancomycin-resistant *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Escherichia coli* (Edmiston et al., 2006, Rothenburger et al., 2002). Vicryl Plus sutures (VPS) which are impregnated in triclosan have recently been shown to reduce bacterial adherence to sutures and reduce microbial viability both in vitro and in animal models (Edmiston et al., 2006, Gomez-Alonso et al., 2007, Rothenburger et al., 2002, Storch et al., 2002a, Storch et al., 2002b) with a high safety margin, little or no risk of allergic reactions and no evidence of microbial resistance (Barbolt, 2002, Gilbert and McBain, 2002). In human subjects, evidence has consistently been in favour of VPS in relation to cost and safety profile. Its effect on wound healing and infection rates has also been investigated with positive findings in all of the meta-analyses conducted despite most of the evidence coming from abdominal surgery (Apisarnthanarak et al., 2015, Daoud et al., 2014, Guo et al., 2016, Wang et al., 2013). A

number of trials have also suggested a positive effect of triclosan coated sutures (Nakamura et al., 2013, Thimour-Bergstrom et al., 2013). For example, Ford (Ford et al., 2005) reported in an RCT, which included 147 paediatric patients who underwent general surgical procedures, that VPS decreased postoperative pain, with overall comparable wound handling parameters, when compared to standard vicryl sutures. Justinger (Justinger et al., 2009) used the VPS for abdominal wall closure in >2,000 patients in a prospective study, concluding that using it decreased the rates of wound infections after a midline laparotomy from 10.8% to 4.9% ($P<0.001$). In an RCT of 856 patients, Justinger (Justinger et al., 2013) showed that triclosan impregnation of a 2-0 polydioxanone closing suture can decrease wound infections in patients having a laparotomy for general and abdominal vascular procedures. Similarly, Rozzelle (Rozzelle et al., 2008) conducted an RCT on 84 patients, comparing infection rates in cerebrospinal-fluid shunt-implantation wound closure, using VPS or standard vicryl sutures. The results were again in favour of the VPS, with an infection rate of 4.3% versus 21% in the control group. Fleck (Fleck et al., 2007) conducted a retrospective study on 479 cardiac patients undergoing sternal wound closure, using the two types of sutures, and found that all 28 patients who developed infection were in the standard wound closure group. Mingmalairak (Mingmalairak et al., 2009) conducted an RCT comparing the two types of sutures in patients undergoing appendicectomy, the preliminary report of 100 patients showed no significant difference in surgical site infection (SSI) rates, with the authors further concluding that the use of VPS is safe and satisfactory in surgical practice.

In the National Health Service (NHS), there has been a recent shift in practice in many hospitals whereby VPS has become the suture of choice for wound closures in different surgical specialties including Orthopaedics assuming that benefits outweigh any disadvantages. In Orthopaedics however, no trials to date have investigated the benefits of using VPS for wound closures.

We therefore hypothesised that VPS will be associated with better wound healing characteristics compared to the vicryl sutures, and as a result may potentially be more appropriate for total hip and total knee arthroplasty wound closures.

2.2 Patients and Methods

A single-centred, double-blind RCT has been conducted to compare the healing characteristics of wounds closed using VPS and standard vicryl sutures in patients undergoing primary total hip or total knee arthroplasty. The protocol for the study was approved by the local Research and Development (R&D) department and Regional Ethics Committee (REC) and written informed consent was obtained from all patients.

2.2.1 Patient Selection Criteria

Patients listed for a primary hip or knee arthroplasty under the care of one surgical team at University College London Hospital (UCLH) constituted the study groups for the trial.

a) Inclusion criteria:

Adult patients (age≥18 years) undergoing unilateral primary total hip or knee arthroplasty

b) Exclusion criteria:

1) Unilateral primary total hip or knee arthroplasty performed for trauma
2) Revision procedure or a previous incision in the operative field
3) History of tendency for keloid formation
4) Allergy to triclosan/vicryl
5) Bleeding tendency (e.g. haemophilia and platelet disorders) or being on regular anticoagulation treatment (e.g. warfarin, treatment dose of low molecular weight heparin (LMWH) or conventional heparin)
6) Underlying malignancy and immunocompromised status
7) Dementia and mental illnesses preventing informed consent
8) Children (age<18years)

Permitted therapies included:

1. Aspirin
2. Subcutaneous prophylactic conventional or LMWH

2.2.2 Patient Recruitment

Patients were approached to participate in the trial at the pre-assessment clinic 3 weeks before their operation by a member of the research team who attended the clinic. The trial was discussed with them and the written information sheet supplied (Appendix 2.1). Contact numbers of the research team were provided if patients wanted to discuss any issues before they participated in the trial. On admission, patients were given the opportunity to ask any further questions and were invited to sign the consent form (Appendix 2.2). Non English speakers were provided with translators. It was explained that there was no requirement to participate and that refusal would not prejudice continued care in any way. The general practitioners of the recruited patients were informed by a postal letter (Appendix 2.3).

2.2.3 Trial interventions

Participants were randomly assigned to receive coated polyglactin 910 sutures with triclosan (Vicryl Plus; Ethicon, Inc.) or conventional sutures (coated polyglactin 910 – Vicryl; Ethicon, Inc.). The operations were performed according to the senior surgeon's (FSH) default procedures which include using a medial parapatellar approach and cemented TKAs and a posterior approach and uncemented THA prostheses. Closure of the TKA wounds included using interrupted 1 vicryl/VPS for the medial parapatellar incisions and 2-0 vicryl/VPS for the subcutaneous tissues followed by skin clips. Closure for the THA wounds included using interrupted 1 vicryl/VPS for the fascia lata and 2-0 vicryl/VPS for the subcutaneous tissues followed by skin clips. For TKAs, a tourniquet was only inflated at the time of cementation and was released after dressing the wound. No drains were used. Antibiotic prophylaxis

included 3 doses of intravenous cefuroxime 750mg or alternatively 2 doses of teicoplanin 400mg if the patient was allergic to cefuroxime, with the first dose given at induction of anaesthesia and the rest within the first 24 hours from the operation. All patients received anti-embolism stockings as well as LMWH for thromboprophylaxis. Perioperative care plans were similar for each type of operation.

2.2.4 Randomisation and blinding

Randomisation and blinding were performed by SealedEnvelope Ltd. with assignment of letter codes to study and control groups. The suture type corresponding to a particular letter code was known only to the member of team who received the codes and was not part of the operating surgeons as well as the operating room nurses. An equal number of study and placebo letter code cards were prepared and placed individually in sealed envelopes. The nurses used consecutive allocation which was concealed from all professionals delivering patient care. Participants and investigators were blinded to treatment assignment (double-blinded study), because study and placebo sutures are indistinguishable after removal of the package labelling by the nurses.

Block randomisation was used, with unequal block sizes in order to keep the sizes of treatment groups similar. The randomisation schedule was performed by SealedEnvelope Ltd. Randomisation codes were only broken in a case of a serious adverse event according to SealedEnvelope Ltd. protocol of unblinding as detailed in the data monitoring section.

2.2.5 Outcome Measures

a) ***Primary outcome:***

The primary outcome was the ASEPSIS wound scoring system devised by Professor Wilson in 1986 at UCLH (Wilson et al., 1986). ASEPSIS is a quantitative wound scoring method and is calculated using objective criteria based both on visual

characteristics of the wound and the consequences of infection (Tables 2.1 and 2.2). A score of > 10 indicates an increasing probability and severity of infection (Table 2.3). The ASEPSIS scoring system has been shown to be both objective and repeatable (Wilson et al., 1986, Bruce et al., 2001, Wilson et al., 2004). The reason for choosing the ASEPSIS scoring system was to analyse the wound healing characteristics for the sutures included in the study with an assessment of infection risk as a higher ASEPSIS score is indicative of various severities of an infection.

Table 2.1 Points scale used to calculate total ASEPSIS score

Criterion	**Points**
Additional treatment	
Antibiotics	10
Drainage of pus under local anaesthetic	5
Debridement of wound under general anaesthetic	10
Serous discharge	0 to 5
Erythema	0 to 5
Purulent exudate	0 to 10
Separation of deep tissues	0 to 10
Isolation of bacteria	10
Stay in hospital over 14 days	5

Table 2.2 Points scale for ASEPSIS daily wound inspection

	Proportion of wound affected (%)					
	0	**> 0 to19**	**20 to 39**	**40 to 59**	**60 to 79**	**80 to 100**
Serous exudate	*0*	*1*	*2*	*3*	*4*	*5*
Erythema	*0*	*1*	*2*	*3*	*4*	*5*
Purulent exudates	*0*	*2*	*4*	*6*	*8*	*10*
Separation of deep tissues	*0*	*2*	*4*	*6*	*8*	*10*

Table 2.3 Breakdown of ASEPSIS scores

Score	Meaning
0 to10	No infection Normal healing
11 to 20	Disturbance of healing
21 to 30	Minor infection
31 to 40	Moderate infection
≥ 41	Severe infection

b) Secondary Outcomes:

- Time for wound closure: Defined as the time period in minutes after insertion of the prosthesis and commencing closure of the fascia in case of THAs or retinaculum for TKAs until completion of skin clips insertion.
- Length of operation in minutes
- Length of hospital stay in days
- Pain assessment using the visual analogue scale scores (1-10) measured at 1, 3 and 5 days postoperatively.
- Complications (see section on adverse events)

2.2.6 Data Processing

Research team members (MS, DG, AG and RK), collected the data and stored it on a modified Excel 97 database in accordance with the data protection act using a password protected computer in a locked office. The data was only accessible to members of the clinical care team and all records are being stored for 20 years in a locked file storing cabinet. A data collection form has been devised (Appendix 2.4). Data collected on the form include:

1) ASEPSIS scoring:

Wounds have been assessed by a member of a specialist team, made up of a nurse and three healthcare assistants. The sole role of this team was to collect and record data on wound healing according to ASEPSIS and all members had already received specialist training in the different definitions and diagnosis of surgical site infection. They were blinded to the type of suture used. Microbiology tests, such as wound swabs or tissue cultures, were performed according to clinical judgement. No specific microbiology tests were requested for the study purposes alone. Surgical wounds were inspected two or three days after the operation and again on days four or five if the patient was still in hospital. The proportion of each wound exhibiting erythema, serous discharge, purulent discharge or dehiscence have been recorded. At each post-operative visit, the notes and drug charts of each patient were inspected. The diagnosis of a wound infection by a medical practitioner, the prescription of prophylactic or therapeutic antibiotics and the opening of a wound or drainage of an abscess were recorded. Raised WBC and inflammatory markers are common after THA and TKA. Microbiology swabs can be contaminated and can be inconclusive.

At the time of discharge patients were given a simple 'yes/no' questionnaire regarding their wound, which they have been asked to complete and return in a pre-paid envelope two months later. Patients were contacted by telephone if no postal questionnaire was returned. The questionnaire was used to ascertain whether a wound infection had been diagnosed since discharge, whether antibiotics had been prescribed for the wound, whether any further surgery had been necessary and whether the hospital stay had been longer than 14 days. Additionally, each patient attended our arthroplasty clinic at UCLH at 2 and 6 weeks postoperatively for assessment of the wound and any additional treatment necessary. A single patient episode was defined as an operation with follow-up of either 2 months or until a further operation is

performed, whichever is shorter. At any time point, surgical site infection resulting in readmission was recorded in the database.

2) Patients' demographics, risk factors affecting wound healing, surgical data and postoperative complications:

   These were collected for baseline comparison of the study groups through attendance of pre-assessment clinics, operative lists and follow-up clinic appointments. Risk factors affecting wound healing included operative time and patient age, gender, body mass index, diabetes, smoking and performance level classified according to the ASA grade (Keats, 1978).

2.2.7 Statistical Analysis and Data Monitoring

PR, Senior Research Associate, Biostatistics group, Joint University College London/Royal Free Biomedical Research Unit, was involved in the design of the study and carried out the sample size calculation in Stata 11. MS analysed the results in SPSS 21.

Data from 319 patients who had received the standard vicryl suture was available. These patients had an ASEPSIS score ranging from 0 to 33. A clinically significant difference as discussed with Professor Wilson who devised the ASEPSIS scoring system would be the VPS reducing the ASEPSIS score by 10 as this is equivalent to reducing the scores by a category (i.e. moderate to minor infection). If the VPS reduced all patients with a score of 11 to 20 to 10 and below and everyone else to a score 10 lower, then we would expect 97.5% of patients to score 10 and below. Sample size calculations were performed under the following assumptions: a two group RCT with equal group sizes, 90% of patients on the standard vicryl suture to have a score of ten and below and 97.5% of patients with the VPS to have a score of 10 and below, two sided 5% significance, 80% power, and 10% dropout. 210 patients are required in each group. We anticipated recruitment over 24 months.

Recruitment and progress through the study has been summarised using a Consort diagram as detailed in the Results section. The two study groups' baseline characteristics were compared using means and standard deviations for continuous data and frequency counts and percentages for categorical data. The primary outcome which is the binary variable ASEPSIS score ten and below versus score 11 and over has been analysed with a chi-squared test for a 2x2 contingency table. If the two study groups were not comparable then the primary outcome was further analysed with logistic regression including the baseline characteristics as co-variates. The primary outcome score was also analysed with the Mann-Whitney U test as a secondary sensitivity analysis. Continuous secondary outcomes such as time for wound closure, length of operation and hospital stay were analysed with the Mann-Whitney U test. Categorical secondary outcomes such as postoperative complications were analysed with the Fisher exact test. The proportion of dropouts from the study and adverse events were reported. Data analysis was done on an intention to treat basis. All statistical analyses were performed with SPSS version 21.0 software (SPSS, Inc.). Randomisation codes were broken only in the case of a serious adverse event and this was documented and discussed with the data monitoring committee and sponsor according to the unblinding protocols set up by SealedEnvelope Ltd. without discontinuing the trial. The data monitoring committee included Professor Wilson and members of his team who were not directly involved in conducting the study.

2.2.8 Withdrawal from the trial

All patients were permitted to withdraw from the study at any point without prejudice to the routine care available.

2.2.9 Safety profile

Adverse Reaction (AR): Means any untoward and unintended response in a participant to the VPS as stated in the Summary of Product Characteristics (SmPC).

Adverse reactions associated with the use of this device include:

1. Wound dehiscence
2. Minimal acute inflammatory tissue reaction
3. Localised irritation
4. Suture extrusion and delayed absorption in tissue with poor blood supply
5. Allergic reaction to triclosan
6. Calculi formation in biliary and urinary tracts when prolonged contact with salt solutions such as bile and urine occurs

Adverse Event (AE): Any untoward medical occurrence in a participant to whom the study drug has been administered and which does not necessarily have a causal relationship with this treatment. These include the complications of THA and TKA as well as ARs mentioned above. The followings have been reported as potential complications:

1. Nausea and Vomiting
2. Dizziness
3. Pain (acute and chronic)
4. Bleeding
5. Stiffness
6. Neurovascular injuries
7. Deep venous thrombosis
8. Chest infection
9. Pulmonary embolism

10. Myocardial infarction
11. Cerebrovascular accidents
12. Infection
13. Fracture
14. Dislocation
15. Loosening of the prosthesis
16. Death

Serious Adverse Event (SAE) or *Serious Adverse Reaction (SAR):* Means any of the above AEs or ARs respectively that:

1. results in death; or
2. is life threatening;
3. requires hospitalisation or prolongation of existing hospitalisation;
4. results in a persistent or significant disability or incapacity
5. consists of a congenital anomaly or birth defect in offspring of subjects or their partners taking the study drug regardless of time of diagnosis
6. Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered serious adverse events when, based on appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include acute renal failure, allergic bronchospasm requiring intensive treatment or blood dyscrasias.

Suspected Serious Adverse Reaction (SSAR): means one of the above mentioned adverse reactions of the VPS that is classed in nature as serious which is consistent with the information about the medicinal product listed in the relevant reference documentation (SmPC).

Unexpected Adverse Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction (SUSAR): means an adverse reaction that is classed in nature as serious and which is not consistent with the information about the VPS.

Other Safety Issues considered to be Serious: Other safety issues where they might materially alter the current benefit-risk assessment of the medical device or that would be sufficient to consider changes in the medical device administration or in the overall conduct of the trial also need to be considered serious, for instance:

a. an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important,
b. post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the Sponsor,
c. new events related to the conduct of the trial or the development of the medical device and likely to affect the safety of the subjects, such as:
    - an SAE which could be associated with the trial procedures and which could modify the conduct of the trial,
    - a significant hazard to the subject population such as lack of efficacy of a medical device used for the treatment of a life-threatening disease,
    - any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same Sponsor,
d. recommendations of the Data Monitoring Committee, if any, where relevant to the safety of the subjects.

2.2.10 Adverse Events / Reactions Monitoring

The occurrence of serious and non serious AEs and ARs in patients on both trial arms was sought while they were in hospital and at each subsequent hospital visit. Patients were asked about hospitalisations, consultations with other medical practitioners, disabilities or incapacity and whether any other adverse events have occurred.

A section in the data collection sheet has been designed to record SAEs as defined above in the complications section. SAEs have been assessed and recorded in the patient's medical notes including the start dates (if known) of the onset of the event as well as the date the event stopped or changed, treatment and outcome; if applicable.

2.2.11 Adverse Events / Reactions Reporting

- Non serious adverse events have not been reported. These are quite common and mostly self limiting in the first few days after surgery.
- Serious adverse events: SAEs have been reported to the principal/chief investigator within 24 hours and evaluated for seriousness, expectedness and severity by them. If there was a significant increase in the incidence of the above SAEs above the reported incidence, the sponsor would have been informed and consulted. The causality of SAE would have been evaluated by the data monitoring committee as above and if causality of these SAEs was linked to the VPS, it would have been reported to the Medicines and Healthcare products Regulatory Agency (MHRA), REC within 7 days if the event was fatal or life threatening or 15 days if the event was not fatal or life threatening.
- In accordance with the European Union directive (article 16 & 17) the principal/chief investigator would have reported SUSARs to the sponsor within 24 hours of

becoming aware of the event. The chief investigator and the sponsor would have reported SUSARs to the MHRA, REC within the required reporting timelines.

We would have provided the following information when reporting an SAE:

1. Protocol identification (Centre number and patient unique identification number)
2. Subject identification (Patient initials, date of birth, sex)
3. The description of the SAE, intervention and the outcome
4. Relevant medical background
5. Any other available information that is requested by the MHRA, REC or the local R&D department

2.2.12 Ethical Considerations

MHRA was contacted and it has been ascertained that the trial did not come under the MHRA regulations as the suture is counted as a medical device, not a pharmaceutical drug. Informed consent has been obtained from patients. (Appendix 2.6)

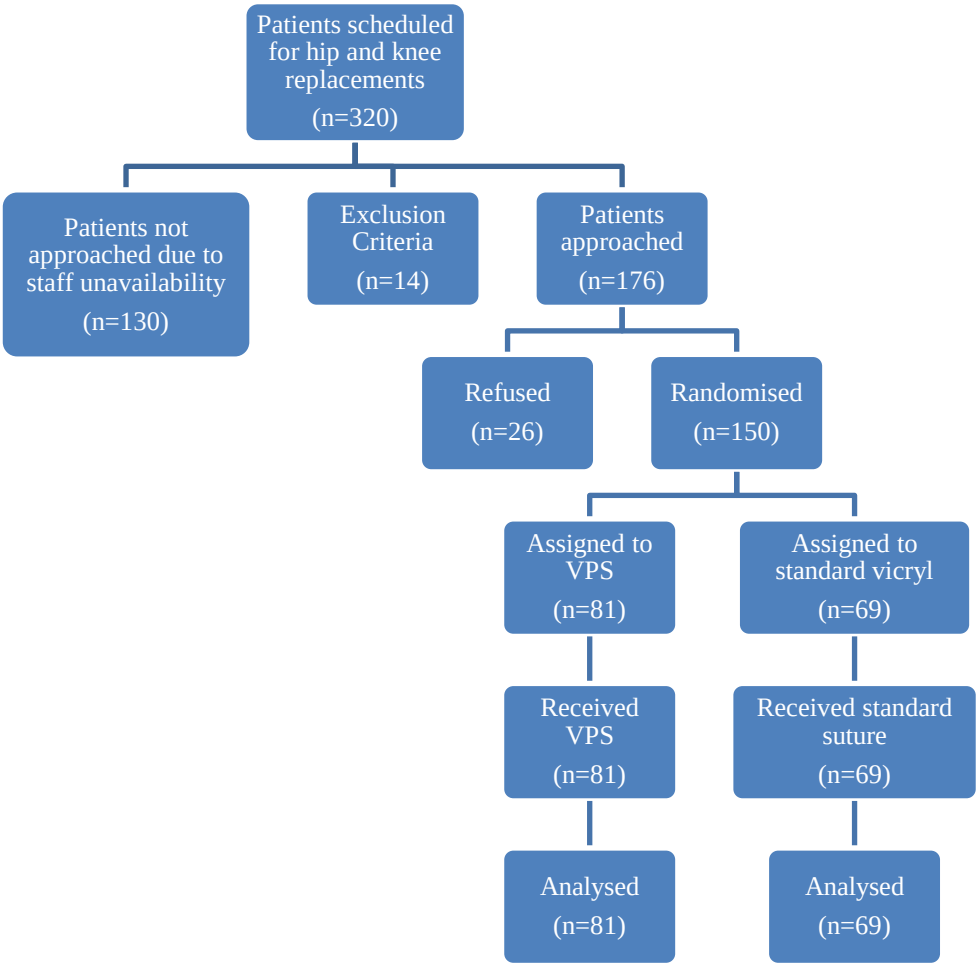
2.3 Results

The trial was started in November 2013 after obtaining the necessary approvals from the UCLH Research and Development department (Appendix 2.7) and the Regional Ethics Committee (Appendix 2.8). It was registered with an International Standard Randomised Controlled Trial Number (ISRCTN) 21430045.

2.3.1 Recruitment and Consort Flow Diagram

Patients were recruited between November 2013 and December 2014. During this period, there were 320 patients scheduled for primary hip and knee replacements. However, 130 patients were not approached at admission due to the non availability of the designated research staff to conduct the study. Fourteen patients were excluded for various reasons such as history of previous trauma accounting for the osteoarthritis, revision surgery or being on warfarin. Twenty six patients refused to take part in the study. Therefore the study consisted of 150 participants, 81 were randomised to the VPS and 61 were randomised to the standard vicryl suture (Figure 2.1). After December 2014, the hospital terminated the contract with Ethicon to move to another supplier and hence the sutures were no more available and the trial had to be ended and results analysed.

Figure 2.1 Consort Diagram of Patients' Recruitment and Allocation



2.3.2 Characteristics of the Study Population

A total of 150 patients were analysed, 81 in the VPS and 69 in the standard group. The mean age was 68 years (SD 10.4). There were 49 males and 101 females and the primary indication for an operation was osteoarthritis in 145 (96%) patients. Although the numbers of cases was planned to be equal, the early termination of the study resulted in unequal numbers in each study group. There were 96 THAs and 54 TKAs performed and the mean length of hospital stay was 6.19 days (SD 4.15). One hundred and forty four patients (96%) completed the follow-up by either attending the 6 weeks outpatient appointment or sending in the post

discharge questionnaire. Demographics and risk factors for wound complications and infection were comparable for the two groups (Table 2.4).

Table 2.4 Patients demographics

		Suture		Statistical significance (p-value)
		Standard (n=69)	VPS (n=81)	
Age	Mean (SD)	67.85 (9.85)	68.65 (10.90)	0.44
Diagnosis	OA	68	77	0.33
	SUFE	0	2	
	AVN	1	0	
	Hip dysplasia	0	1	
	Perthes	0	1	
Gender	Male	24	25	0.73
	Female	45	56	
BMI	Mean (SD)	28.70 (5.13)	29.14 (4.97)	0.54
Smoker	Yes	6	6	0.64
	Never	42	57	
	Ex-Smoker	13	12	
Diabetic	Yes	4	10	0.26
	No	57	64	
ASA Grade	1	9	9	0.68
	2	47	52	
	3	13	20	

OA: Osteoarthritis, SUFE: Slipped upper femoral epiphysis, AVN: Avascular necrosis, BMI: Body mass index, ASA: American Society of Anesthesiologist

2.3.3 Operative Data

There were 96 THAs and 54 TKAs performed during the study. However, the procedures were balanced between the 2 arms of the trial (P =0.5). A Synergy-R3, Smith & Nephew and Trinity-TriFit TS, Corin were used for cementless THAs whereas in 3 cases a cemented Exeter was implanted as per surgeon's preference. For TKAs, Triathlon, Stryker was used for the majority of cases and SAIPH® Knee, MatOrtho® were used in some cases. The majority of the operations were performed by registrars (n=79) followed by the consultant (n=54) and then fellows (n=17) but again this was balanced between the 2 arms of the trial (P =0.63). The majority of patients underwent a general anaesthetic (95 patients). Cefuroxime was the prophylactic antibiotic used for most operations and teicoplanin was administered to penicillin allergic patients occasionally in combination with gentamicin. The length of operation was 91.24 minutes (SD 26.5) in the VPS group and 88.44 minutes (SD 23.84) in the standard vicryl group (P=0.67). An average of 4 sutures were used for wound closures in both groups and there was no significant difference in wound closure time between the study groups (VPS 13.89 (SD 5.13), standard vicryl 14.64 (SD 5.51), P=0.47). (Table 2.5)

Table 2.5 Operative Data

		Suture		Statistical significance (p-value)
		Standard (n=69)	VPS (n=81)	
Site	Hip	42	54	0.5
	Knee	27	27	
Surgeon	Consultant	25	29	0.63
	Registrar	38	41	
	Fellow	6	11	

Anaesthetic	General	45	50	
	Regional	17	26	0.56
	Both	3	2	
Local anaesthetic	Yes	67	77	0.38
	No	1	4	
Antibiotic	Cefuroxime	62	74	0.74
	Cefuroxime + Gent	0	1	
	Teicoplanin + Gent	1	1	
	Teicoplanin	3	2	
Length of operation	Mean (SD)	88.44 (23.84)	91.24 (26.5)	0.67
Number of sutures used	Mean (SD)	3.75 (0.87)	3.53 (0.81)	0.12
	2	1	7	0.26
	3	23	29	
	4	30	30	
	5	6	8	
	>5	1	0	
Prosthesis Hip	Synergy – R3	37	48	0.30
	Trifit – Trinity	3	3	
	Exeter	0	3	
Knee	Triathlon	21	23	0.70
	Saiph Knee	5	3	
Wound closure (mins)	Mean (SD)	14.64 (5.51)	13.89 (5.13)	0.47
VAS Score	Day 1	6.47 (2.62)	6.20 (2.35)	0.34
(Mean, SD)	Day 3	4.75 (2.33)	4.18 (2.33)	0.15
	Day 5	4.67 (1.75)	2.92 (2.87)	0.18
Length of stay	Mean (SD)	6.13 (4.23)	6.23 (4.11)	0.95

Gent: Gentamicin, VAS: Visual analogue scale

2.3.4 Postoperative Outcomes

2.3.4.1 Wound Outcomes

Surgical wounds were scored using ASEPSIS two or three days after the operation and again on days four or five if the patient was still in hospital. The scores were further adjusted at the 2 and 6 weeks follow up appointments and on receiving the post discharge questionnaire if any additional procedures were performed including the administration of antibiotics or drainage/washout of the wound. The binary variable ASEPSIS score ten and below versus score 11 and over has been analysed with a chi-squared test for a 2x2 contingency table and this showed no significant difference between the study groups as there were only 6 cases in the VPS group and 4 in the standard group who scored above 10 (P=0.75). However, the primary outcome score was also analysed with the Mann-Whitney U test as a secondary sensitivity analysis and this showed a significant difference in the scores among the study groups (VPS 2.54 vs. standard suture 1.41, P=0.036). Additionally, wound complications were also documented at the follow up appointments. At 2 weeks, there were 6 wound related complications in the VPS group including 2 superficial infections requiring antibiotics, a leaking wound and erythema surrounding the wounds in 3 cases whereas one case in the standard vicryl group needed oral antibiotics for a superficial infection (P=0.22). At 6 weeks, there were 8 wound related complications in the VPS group including 3 superficial infections requiring oral antibiotic treatment, one wound dehiscence, irritation from the suture in 2 cases, persistent wound discharge in one case and deep wound infection requiring washout of the wound and exchange of the liner in a THA in one case. In the standard vicryl group, there was only one case which required oral antibiotics for a superficial wound infection at the 6 weeks follow up appointment (P=0.03). (Tables 2.6, 2.7 and 2.8)

Table 2.6 ASEPSIS Scoring

		Suture		Statistical significance (p-value)
		Standard (n=69)	Triclosan (n=81)	
ASEPSIS Scores for groups	0-10 >10	65 4	75 6	0.75
ASEPSIS Scores	Mean (SD)	1.41 (0.38-2.43)	2.54 (1.41-3.68)	0.036

Table 2.7 Follow-up outcomes (2-week)

		Suture		Statistical significance (p-value)
		Standard (n=69)	Triclosan (n=81)	
Attended follow-up	Hospital Community Inpatient Did not attend	35 27 2 5	37 28 10 6	0.21
Wound complications	Yes No	1 63	6 69	0.22
	Superficial SSI Erythema Leaking wound	1 0 0	2 3 1	

SSI: Superficial site infection

Table 2.8 Follow-up outcomes (6-week)

		Suture		Statistical significance (p-value)
		Standard (n=69)	Triclosan (n=81)	
Attended hospital	Yes	61	65	0.189
	No	8	16	
Wound Complications	Yes	1	8	0.03
	No	60	57	
	Superficial SSI	1	3	
	Wound dehiscence	0	1	
	Irritation from suture	0	2	
	Serous discharge from wound	0	1	
	Deep SSI	0	1	
Complications	Nausea and vomiting	0	2	0.12
	Dizziness	0	0	1
	Bleeding (not from wound)	1	2	0.26
	Stiffness	4	5	0.30
	Neurovascular injury	0	0	1
	DVT	1	0	0.18
	PE	0	1	0.19
	Chest infection	1	2	0.26
	MI	0	0	1
	CVA	0	0	1
	Fracture	0	2	0.12
	Dislocation	0	0	1
	Loosening	0	0	1
	Mortality	0	0	1
	Missing data	8	16	

SSI: Surgical site infection

As planned, the primary outcome was further analysed with logistic regression including the baseline characteristics as co-variates as well. However, this did not show any significant effects of the potential risk factors for wound healing neither in the linear or the multiple regression analysis models. (Table 2.9)

Table 2.9 Regression Analysis of Risk Factors for Wound Complications

	Regression Analysis	
	Linear	**Multiple**
Age	0.28	0.552
ASA	0.347	0.534
BMI	0.508	0.162
Diabetes	0.723	0.990
Gender	0.689	0.842
Length of Operation	0.124	0.182
Number of Sutures	0.628	0.232
Smoking	0.311	0.546
Time for Wound Closure	0.597	0.142
Type of Anaesthesia	0.092	0.394

ASA: American Society of Anesthesiologist, BMI: Body mass index,

2.3.4.2 Visual Analogue Scores and Length of Hospital Stay

There were no differences in the visual analogue scores measured on days 1, 3 and 5 or the length of hospital stay which averaged 6.23 days in the VPS group and 6.13 days in the standard vicryl group (P=0.95). (Table 2.2)

2.3.4.3 Complications

Systemic complications occurring in the VPS group included nausea and vomiting in 2 patients, gastrointestinal bleeding in two patients who underwent an endoscopy to treat an underlying gastric and duodenal ulcers, stiffness of the operated joint in 5 cases which was treated conservatively, two chest infections treated with antibiotics, one pulmonary embolism treated with LMWH then warfarin, a calcar fracture treated intraoperatively and an undisplaced greater trochanteric fracture noted postoperatively which was treated conservatively with protected weightbearing. Complications in the standard vicryl group included a patient who had melaena secondary to a duodenal ulcer which resolved spontaneously, stiffness of the operated joint in 4 patients which was treated conservatively, one chest infection treated with antibiotics and one deep vein thrombosis treated with LMWH then warfarin (P=0.24).

2.4 Discussion

Due to the popularity of the VPS assuming its superiority in preventing infections and wound complications, it has become widely used in various surgical specialties even when the evidence is lacking. Therefore, we conducted this RCT to compare the wound healing characteristics of VPS and standard vicryl sutures in primary THA and TKA surgery. Despite the premature termination of this study due to the unavailability of the sutures after December 2014, the study findings were significant to reject our hypothesis that the VPS will be associated with better wound healing characteristics and fewer infections than standard vicryl sutures. Although the binary variable ASEPSIS score ten and below versus 11 and over was insignificant, this may be related to a type II error due to an underpowered study. However, sensitivity analysis using the Mann Whitney test (P=0.036) as well as assessment of the wound complications at the last follow up showed significantly higher wound complication rates in the VPS group (P=0.03).

Although the majority of evidence in the literature supports the use of VPS in surgical wound closures, there have been some studies published recently which questioned its efficacy and higher complication rates. For example, Mattavelli (Mattavelli et al., 2015) conducted a multi-centred RCT including 281 patients on the effect of triclosan coated sutures on SSI after colorectal surgery. The rate of SSI was reported as 12.9% (18/140) in the triclosan group versus 10.6% (15/141) in the control group (odds ratio: 1.24; 95% confidence interval: 0.60-2.57; p=0.564). Additionally, the overall incision complication rate was 45.7% in the triclosan group vs. 38.3% in the control group (odds ratio: 1.36; 95% confidence interval: 0.84-2.18; p=0.208). Another multi-centered RCT (Diener et al., 2014) investigating the effectiveness of triclosan-coated PDS Plus versus uncoated PDS II sutures for prevention of SSI after abdominal wall closure in 1224 patients showed that

triclosan-coated PDS Plus did not reduce the occurrence of surgical site infection. Similarly, a beneficial effect of triclosan against Gram positive bacteria could not be confirmed in another RCT comparing wound infection rates after colon and rectal surgeries in 485 patients (Huszar et al., 2012). Deliaert (Deliaert et al., 2009) conducted an RCT on 26 patients undergoing bilateral breast reduction surgery to evaluate wound dehiscence rates. Wound dehiscence occurred in 16 cases among the triclosan breast versus seven cases only in the control breast (McNemar test $p = 0.023$). Another RCT (Seim et al., 2012) reporting on wound closures in the lower limb showed that triclosan-coated sutures do not reduce leg wound infections after coronary artery bypass grafting with an infection rate of 10.0% (16/160) in the VPS group and infection rate of 10.4% (17/163) in the standard vicryl group ($P = 1.00$). The discrepancy in the effect of triclosan coated sutures among studies which dealt with abdominal surgery may relate to the microorganisms that differ substantially in different populations according to alimentary habits and environmental conditions (Hold, 2014, Power et al., 2014). Other causes proposed include study design such as type of suture, the use of interrupted versus continuous sutures, single-layer abdominal closure and skin closure. Although triclosan has been associated with low systemic toxicity in a number of studies, negative effects such as dermatitis, skin irritation, allergic reactions and haematomas have been described (Fiss et al., 2007, Mattavelli et al., 2015). In hip and knee replacement surgery where rates of SSI are low in comparison to abdominal surgery, such effects may become more important as encountered in our study. It is also noteworthy that resistance to triclosan and multidrug resistance have recently been linked to the increase in environmental microbial communities exposed to triclosan and that there are plans proposed to quantitatively define the conditions under which triclosan selects for multidrug resistance in the environment (Carey and McNamara, 2015).

There are several strengths of this RCT. First, we conducted a double blinded RCT according to strict inclusion and exclusion criteria to address the intervention of interest. Second, this is the first RCT with reported outcomes in the literature investigating the effect of VPS on THA and TKA wounds. Third, the results of this RCT were consistent with a negative effect of VPS on wound closures after hip and knee arthroplasties.

Limitations of this study include the premature termination of the trial due to the unavailability of the sutures after December 2014 which may have predisposed to a type II error as previously outlined. The duration of follow up is also short but this reflects the protocol for wound surveillance according to the ASEPSIS scoring system which addresses acute infections only. A longer follow up would be necessary to monitor for late infections.

2.5 Conclusion

In summary, the VPS has not been associated with better wound healing characteristics or fewer infections than standard vicryl sutures. Had the VPS group experienced a positive effect on the wounds, a much larger trial would have been required to show a statistically significant difference in wound healing characteristics. However, this study provides a valid basis for further investigation in a larger RCT.

Chapter 3

The Effect of Tranexamic Acid on Wound Healing in Primary Total Hip Arthroplasty: A Meta-analysis

3.1 Introduction

THAs are associated with considerable blood loss and numerous studies have shown that allogeneic blood transfusion increases the risk of SSIs through the mechanism of immunomodulation (Bloch et al., 2013, Friedman et al., 2014). The rates of SSI and lower and upper respiratory tract infections were significantly increased after total hip or total knee arthroplasty in more than 12,000 patients receiving allogeneic blood transfusion compared with those receiving autologous blood transfusion or no blood transfusion (Friedman et al., 2014). On the other hand, the role of autologous transfusion in the risk of developing SSI and PJIs remains inconclusive. Taken together, much effort should be exercised perioperatively to reduce the need for any type of blood product transfusion.

A variety of blood-conserving techniques have been developed to decrease blood loss and postoperative transfusion rates including controlled hypotension, regional anaesthesia, intraoperative blood salvage, erythropoietin and antifibrinolytic agents (Rajesparan et al., 2009, Cardone and Klein, 2009). Antifibrinolytics which include tranexamic acid (TXA), aprotinin and epsilon aminocaproic acid (EACA) utilise different mechanisms to inhibit the dissolution of blood clots. They have been successfully used to stop bleeding after dental extractions, tonsillectomies, prostate surgery, heavy menstrual bleeding, cardiac surgery and in patients with haemophilia. Numerous studies have also investigated their efficacy in reducing blood loss and transfusion requirements in THA with no extra risk. However, no studies to date have investigated the direct relationship between antifibrinolytics and wound complications including SSIs.

TXA has gained significant popularity in reducing perioperative blood loss, particularly after the publication of the Bart's study (Fergusson et al., 2008). It is cheaper and safer than aprotinin and much more potent than EACA with overall good penetration into major joints (Ellis et al., 2001, Good et al., 2003).

Therefore, the purpose of this systematic review and meta-analysis was to investigate the hypothesis that TXA may be associated with less wound complications including SSIs after primary THA.

3.2 Materials and Methods

The methods for this study were based on the Cochrane methodology for conducting systematic reviews and meta-analyses (Higgins and Green).

3.2.1 Study Selection Criteria

3.2.1.1 Types of Studies

RCTs and quasi-randomised controlled trials (for example, allocation by hospital number or date of birth) trials have been considered for this review.

3.2.1.2 Types of Participants

The participants were adults who underwent THA regardless of the type or size of prosthesis used.

3.2.1.3 Types of Interventions

The intervention considered was the administration of intravenous TXA. Studies involving the administration of TXA by oral, topical or intramuscular route or comparing those to the intravenous route were excluded. Only studies with a control group were considered. The control group received a placebo, another antifibrinolytic agent or no treatment.

3.2.1.4 Types of Outcome Measures

The primary outcome measure was:

Wound complications including infections

The secondary outcome measures were:

1. Intraoperative, postoperative and total blood loss

2. The proportion of patients who had allogeneic blood transfusion. Hence, studies where autologous blood was systematically re-infused to part or all of their patients were not included in measuring this outcome in order to decrease bias.
3. The amount of blood units transfused per patient
4. Functional hip outcome measures (e.g. Oxford hip score)
5. General quality of life outcome measures (e.g. SF 12, SF 36 or EUROQOL)
6. Complications such as: Deep venous thrombosis (DVT), pulmonary embolism (PE), any thrombosis, renal failure, reoperation due to bleeding, non-fatal myocardial infarction, stroke and death.

3.2.2 Search Methods for Identification of Studies

The following exploded MeSH terms have been used for the initial literature search: "Antifibrinolytics", "Tranexamic acid", "Cyklokapron", "Aprotinin", "Trasylol", "Epsilon aminocaproic acid" and "Amicar". The Medline search was then refined to clinical trials and RCTs in human adults. Results were cross checked with other databases, namely EMBASE, the Cochrane Controlled Trials Register, HealthSTAR and CINAHL, Google and Google scholar for trials of antifibrinolytics and THA published in any language from 1966 to April 2016.

The bibliographies of retrieved trials and other relevant publications, including reviews and meta-analyses, were cross-referenced for additional articles. The following websites were searched to identify unpublished and ongoing studies: Current Controlled Trials (www.controlled-trials.com); Centre Watch (www.centerwatch.com); Trials Central (www.trialscentral.org); The UK National Research Register (www.nres.nhs.uk/researchsummaries). Journal of Bone and Joint Surgery - British Volume

(now the Bone and Joint Journal) and American Volume (www.ejbjs.org), and the American Academy of Orthopaedic Surgeons (www.aaos.org) were searched manually.

3.2.3 Data Collection and Analysis

3.2.3.1 Selection of the Studies

Two authors (MS&SA) independently applied the search strategy to select references from the aforementioned databases. The article titles and abstracts were reviewed independently. When there was a doubt, the full article was retrieved for further scrutiny. The two authors independently assessed each full study report to see if it met the review's inclusion criteria. Authors were contacted for more information and clarification of data as necessary. Disagreement was discussed with the senior authors (JM&FSH) and when no consensus was reached, the particular study was excluded.

3.2.3.2 Assessment of Methodological Quality of Included Studies

The review authors used a modification of the generic evaluation tool used by the Cochrane Bone, Joint and Muscle Trauma Group (Madhok et al., 2007) (Table 3.1). Two authors (MS&SA) assessed the methodological quality of each study. Disagreement was resolved by the senior authors (JM&FSH). The total quality assessment score (QAS) was reported for each study, however; it was not used to weight the studies in the meta-analysis.

Table 3.1 Quality Assessment Items and Possible Scores
A. Was the assigned treatment adequately concealed prior to allocation? 2 = method did not allow disclosure of assignment 1 = small but possible chance of disclosure of assignment or unclear 0 = quasi-randomised or open list/tables
B. Were the outcomes of participants who withdrew described and included in the analysis (intention to treat)? 2 = withdrawals well described and accounted for in analysis 1 = withdrawals described and analysis not possible

0 = no mention, inadequate mention, or obvious differences and no adjustment
C. Were the outcome assessors blinded to treatment status? 2 = effective action taken to blind assessors 1 = small or moderate chance of unblinding of assessors 0 = not mentioned or not possible
D. Were the treatment and control group comparable at entry? (Likely confounders may be age, partial or total rupture, activity level, acute or chronic injury) 2 = good comparability of groups, or confounding adjusted for in analysis 1 = confounding small; mentioned but not adjusted for 0 = large potential for confounding, or not discussed
E. Were the participants blind to assignment status after allocation? 2 = effective action taken to blind participants 1 = small or moderate chance of unblinding of participants 0 = not possible, or not mentioned (unless double-blind), or possible but not done
F. Were the treatment providers blind to assignment status? 2 = effective action taken to blind treatment providers 1 = small or moderate chance of un blinding of treatment providers 0 = not possible, or not mentioned (unless double-blind), or possible but not done
G. Were care programmes, other than the trial options, identical? 2 = care programmes clearly identical 1 = clear but trivial differences 0 = not mentioned or clear and important differences in care programmes
H. Were the inclusion and exclusion criteria clearly defined? 2= clearly defined 1= inadequately defined 0= not defined
I. Were the interventions clearly defined? 2 = clearly defined interventions are applied with a standardised protocol 1 = clearly defined interventions are applied but the application protocol is not standardised 0 = intervention and/or application protocol are poorly or not defined
J. Were the outcome measures used clearly defined? (by outcome) 2 = clearly defined 1 = inadequately defined 0 = not defined

K. Were diagnostic tests used in outcome assessment clinically useful? (by outcome) 2 = optimal 1 = adequate 0 = not defined, not adequate
L. Was the surveillance active, and of clinically appropriate duration? 2 = active surveillance and appropriate duration 1 = active surveillance, but inadequate duration 0 = surveillance not active or not defined

3.2.3.3 Data Extraction and Management

A data extraction form was designed and agreed by the authors. A pilot test of five articles was performed to ensure the form's consistency. Initially, two authors (MS&SA) extracted the data independently which was later on reviewed jointly to produce agreed accurate data. Disagreements were resolved by consensus or consultation with the senior authors (JM&FSH). Authors of individual trials were contacted directly to provide further information when necessary.

3.2.3.4 Statistical Analysis

Review Manager Database (RevMan version 5.3, The Cochrane collaboration 2014) was used for analysis of the selected studies. Continuous data for each arm in a particular study was expressed as mean and standard deviation and the treatment effect as mean differences. Dichotomous data for each arm in a particular study was expressed as proportions or risks, and the treatment effect as risk differences. Missing data was sought from the authors. Where this was not possible or data was missing through loss to follow-up, intention-to-treat principles were used.

Summary estimates of the overall effect of treatment are provided in the form of a forest plot. The Mantel-Haenszel (M-H) method was used to combine studies using a fixed effects

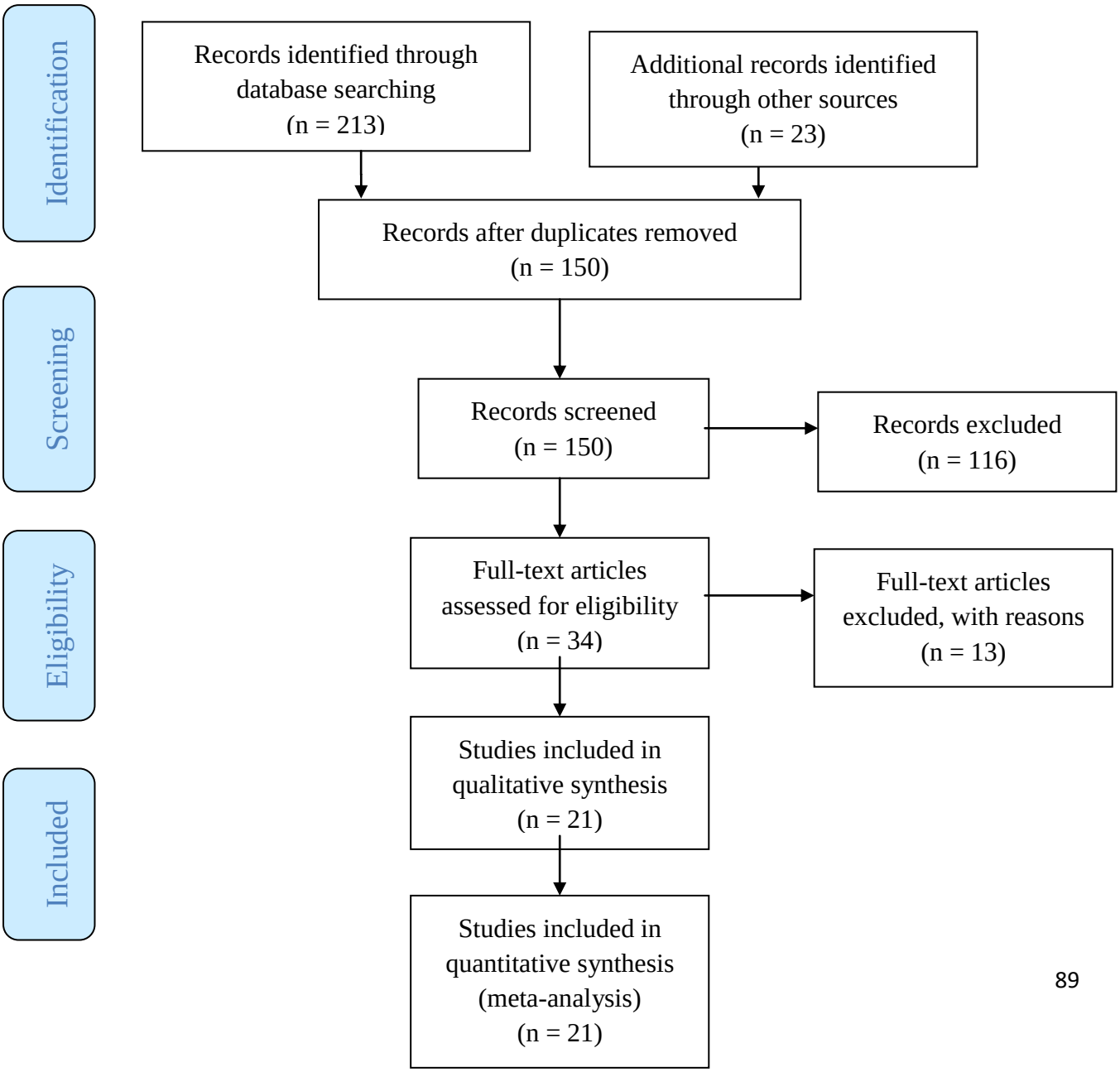
model. The presence of statistical heterogeneity was assessed through Q and I^2 statistics, a value of I^2 >50% being considered substantial heterogeneity. We planned to use funnel plots to assess reporting bias if more than 10 studies measured any particular outcome. We also compared the method descriptions of the included studies with the actual reported outcomes in the results section to assess selective outcome reporting bias.

3.3 Results

3.3.1 Description of Studies

The literature search strategy was applied, then refined and reapplied. Two hundred and thirty six studies were identified as potential relevant studies and subsequent scrutiny of the abstract led to the exclusion of 202 studies. Full publications were obtained for the rest of the studies. These were assessed and 13 further studies were excluded for various reasons according to inclusion and exclusion criteria. (Figure 3.1)

Figure 3.1 PRISMA Chart of the Study Selection Process



Twenty one RCTs were included in the meta-analysis (Claeys et al., 2007, Ido et al., 2000, Niskanen and Korkala, 2005, Garneti and Field, 2004, Benoni et al., 2000, Benoni et al., 2001, Ekback et al., 2000, Husted et al., 2003, Johansson et al., 2005, Lemay et al., 2004, Yamasaki et al., 2004, Barrachina et al., 2016, Hsu et al., 2015, Imai et al., 2012, Jaszczyk et al., 2015, Kazemi et al., 2010, Lee et al., 2013, McConnell et al., 2011, Oremus et al., 2014, Wang et al., 2016, Malhotra et al., 2010). (Table 3.2)

Table 3.2: Characteristics of the Included Studies

Study	N	Intervention	Cementation	DVT prophylaxis	Anaesthesia	Blood transfusion protocol	QAS
Barrachina 2016	72	TXA 15 mg/kg before the operation and saline 3 hours later *Placebo (Saline)*	Uncemented	LMWH	Regional	Hb < 85g/l (fit patient) Hb < 90g/l (elderly patient with comorbidity)	24
Barrachina 2016	71	TXA 10 m/kg before the operation and 10 mg/kg of TXA 3 hours later *Placebo (Saline)*	Uncemented	LMWH	Regional	Hb < 85g/l (fit patient) Hb < 90g/l (elderly patient with comorbidity)	24
Benoni 2000	39	TXA 10 mg/kg at end of operation and 3 hrs later *Placebo (Saline)*	Cemented	LMWH	Regional or General	None	24
Benoni 2001	40	TXA 10mg/kg just before the operation *Placebo (Saline)*	Cemented	LMWH	Regional or General	None	24
Claeys 2007	40	TXA 10mg/kg 15 minutes before operation	Hybrid	LMWH	Regional	Hb < 85 g/l or Hct< 27%	23

		Placebo (Saline)					
Ekback 2000	40	TXA 10 mg/kg just before operation then 1mg/kg/hr infusion over 10 hrs + 10mg/kg further dose after 3 hrs from operation *Placebo (Saline)*	Cemented	LMWH	Regional	Hct <27%	22
Garneti 2004	50	TXA 10mg/kg at induction of anaesthesia *Placebo (Saline)*	Cemented	Mechanical only	Regional	None	24
Hsu 2015	60	TXA 1 gram just before operation and 3 hours after operation *Placebo: (Saline)*	Uncemented	LMWH	General	Hb < 80g/l (fit patient) Hb 80-90g/l (elderly patient with comorbidity)	24
Husted 2003	40	TXA 10 mg/kg just before operation then 1mg/kg/hr infusion over 10 hrs *Placebo (Saline)*	Uncemented or Hybrid	LMWH	Regional	Reduction in Hb>25% and clinical symptoms	24
Ido 2000	40	TXA 1 gram just before operation and 3 hours after operation *Control: None*	Cemented	None	Unknown	None	14
Imai 2012	46	TXA 1 gram before skin closure *Control: None*	Uncemented	LMWH+ mechanical	General and epidural	None	17
Imai 2012	42	TXA 1 gram before skin closure and 6 hours later	Uncemented	LMWH+ mechanical	General and epidural	None	17

		Control: None					
Imai 2012	47	TXA 1 gram before surgery *Control: None*	Uncemented	LMWH+ mechanical	General and epidural	None	17
Imai 2012	48	TXA 1 gram before surgery and 6 hours later *Control: None*	Uncemented	LMWH+ mechanical	General and epidural	None	17
Jaszczyk 2015	124	TXA 15mg/kg just before surgery *Control: None*	Uncemented	LMWH	Regional	None	17
Johansson 2005	100	TXA 15mg/kg just before surgery *Placebo (Saline)*	Cemented	LMWH	Regional	Hb < 90g/l	24
Kazemi 2010	64	TXA 15mg/kg just before surgery *Placebo (Saline)*	Uncemented	LMWH	Regional	None	23
Lee 2013	68	TXA 15 mg/kg just before operation then 15mg/kg infusion until skin closure *Placebo (Saline)*	Uncemented	Not recorded	General and epidural	Hct < 30%	23
Lemay 2004	40	TXA 10 mg/kg just before operation then 1mg/kg/hr infusion until wound closure *Placebo (Saline)*	Cemented or uncemented	LMWH+ mechanical	Regional	Hb < 70g/l (fit patient) Hb < 90g/l (elderly patient with comorbidity)	22
Malhotra 2010	50	TXA 15mg/kg just before surgery *Placebo (Saline)*	Uncemented	LMWH+ mechanical	Regional	None	23
McConnell 2011	44	TXA 10mg/kg just before the operation	Uncemented	Aspirin + Mechanical	General and epidural	None	17

		Placebo (Saline)					
Niskanen 2005	36	TXA 10mg/kg just before the operation then 8 and 16 hours later *Placebo (Saline)*	Cemented	LMWH + mechanical	Regional or General	Hct 0.28-0.30	24
Oremus 2014	42	TXA 1 gram just before operation and 3 hours later *Placebo: (Saline)*	Uncemented	LMWH	Regional	Hb < 80g/l (fit patient) Hb 80-100g/l (if symptoms of anaemia)	24
Wang 2016	77	TXA 10mg/kg just before the operation *Placebo (Saline)*	Uncemented	LMWH + mechanical	General	Hb < 70g/l (fit patient) Hb 70-100g/l (if symptoms of anaemia)	24
Wang 2016	80	TXA 15mg/kg just before the operation *Placebo (Saline)*	Uncemented	LMWH + mechanical	General	Hb < 70g/l (fit patient) Hb 70-100g/l (if symptoms of anaemia)	24
Yamasaki 2004	40	TXA 1 gram just before operation *Control: None*	Uncemented	None	Regional	None	24

The majority were small studies with participant numbers ranging from 36 to 124. However, they were relatively well designed and QAS was high in most of the studies with a mode of 24 (Garneti and Field, 2004, Niskanen and Korkala, 2005, Benoni et al., 2000, Benoni et al., 2001, Husted et al., 2003, Johansson et al., 2005, Yamasaki et al., 2004, Oremus et al., 2014, Wang et al., 2016, Barrachina et al., 2016, Hsu et al., 2015) (the highest possible score) and a range of 14-24. Only one study had a score of less than 20 (Ido et al., 2000). (Table 3.2)

Trials performed were all primary for THA with osteoarthritis as the commonest diagnosis. A placebo (normal saline) was given in 17 studies with only four studies using controls who did not receive any treatment (Yamasaki et al., 2004, Ido et al., 2000, Imai et al., 2012, Jaszczyk et al., 2015). Different doses and modes of TXA delivery were used. The doses ranged from 10-30 mg/kg. The regimen of a single IV bolus given before the operation was used in 10 studies (Claeys et al., 2007, Garneti and Field, 2004, Johansson et al., 2005, Yamasaki et al., 2004, Benoni et al., 2001, Jaszczyk et al., 2015, Kazemi et al., 2010, Malhotra et al., 2010, McConnell et al., 2011, Wang et al., 2016). Six studies used repeated boluses (Ido et al., 2000, Niskanen and Korkala, 2005, Benoni et al., 2000, Barrachina et al., 2016, Hsu et al., 2015, Oremus et al., 2014) and three used a prolonged infusion (Husted et al., 2003, Lemay et al., 2004, Lee et al., 2013). Ekback (Ekback et al., 2000) used a regime of repeated boluses as well as a prolonged infusion and Imai (Imai et al., 2012) trialled different regimes including single and repeated boluses against a saline placebo. All studies except Ido, Yamasaki, Garneti and McConnell (Ido et al., 2000, Garneti and Field, 2004, Yamasaki et al., 2004, McConnell et al., 2011) used LMWH with or without mechanical prophylaxis for DVTs. The former two did not use any chemical prophylaxis, Garneti (Garneti and Field, 2004) used mechanical prophylaxis only and McConnell (McConnell et al., 2011) used a combination of aspirin and mechanical prophylaxis. Eleven studies stated a transfusion trigger which was related to a drop in either haemoglobin or haematocrit levels (Claeys et al., 2007, Niskanen and Korkala, 2005, Ekback et al., 2000, Husted et al., 2003, Lemay et al., 2004, Johansson et al., 2005, Barrachina et al., 2016, Hsu et al., 2015, Lee et al., 2013, Oremus et al., 2014, Wang et al., 2016). There were 12 trials which used solely regional anaesthesia (Claeys et al., 2007, Garneti and Field, 2004, Ekback et al., 2000, Husted et al., 2003, Johansson et al., 2005, Yamasaki et al., 2004, Lemay et al., 2004, Barrachina et al., 2016, Jaszczyk et al., 2015, Kazemi et al., 2010, Malhotra et al., 2010, Oremus et al., 2014), one trial did not

mention the type of anaesthetic used (Ido et al., 2000) and the rest used a combination of general and regional anaesthesia (Niskanen and Korkala, 2005, Benoni et al., 2001, Benoni et al., 2000, Imai et al., 2012, Lee et al., 2013, McConnell et al., 2011). Cemented prostheses were used in 7 trials (Ido et al., 2000, Garneti and Field, 2004, Niskanen and Korkala, 2005, Benoni et al., 2001, Benoni et al., 2000, Johansson et al., 2005, Ekback et al., 2000), uncemented in 11 trials (Yamasaki et al., 2004, Barrachina et al., 2016, Hsu et al., 2015, Imai et al., 2012, Jaszczyk et al., 2015, Kazemi et al., 2010, Lee et al., 2013, McConnell et al., 2011, Oremus et al., 2014, Wang et al., 2016, Malhotra et al., 2010), hybrid in one study (Claeys et al., 2007) and the rest used a combination of cemented, uncemented or hybrid prostheses (Husted et al., 2003, Lemay et al., 2004). The amount of blood units transfused per patient, functional hip and general quality of life outcome measures were not analysed as there was insufficient data to support detailed analysis. No studies reported on mortality in their series of patients. Cost comparison between TXA and blood products was analysed in four studies (Benoni et al., 2001, Niskanen and Korkala, 2005, Johansson et al., 2005, Husted et al., 2003) and favoured the use of TXA.

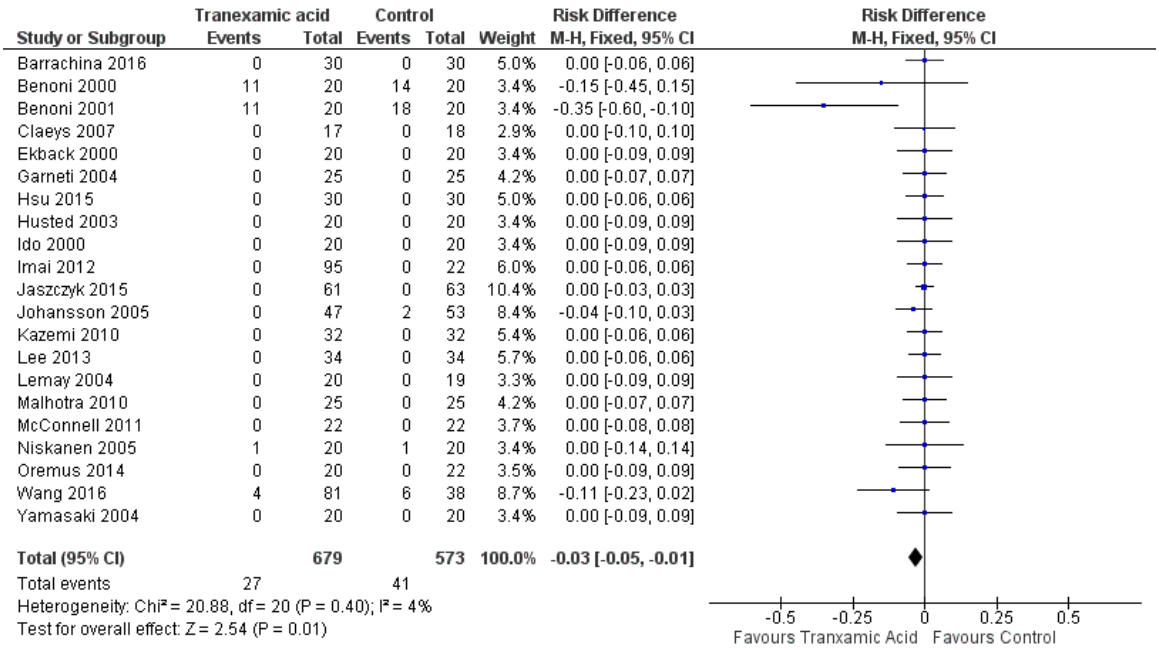
3.3.2 Effects of Interventions

3.3.2.1 Wound Complications including Infections

All studies reported on wound complications and infections which included 679 patients in the TXA group and 573 patients in the control group. There were three infections in the control group and two in the TXA group. Johansson (Johansson et al., 2005) reported two superficial wound infections and Wang (Wang et al., 2016) one in the control group which were treated with antibiotics and no further complications occurred. In the TXA group, one patient developed a superficial infection (Niskanen and Korkala, 2005) and the other a deep infection which was re-operated on after 5 months of the primary procedure (Benoni et al.,

2001). Additionally, 38 wound complications including wound discharge, erythema and haematomas occurred in the control group and 25 in the TXA group (Wang et al., 2016, Benoni et al., 2001, Benoni et al., 2000, Niskanen and Korkala, 2005). Overall, TXA led to a 3% reduction in the risk of developing wound complications including infections compared to the control group with no significant statistical heterogeneity among the study groups (Risk difference -0.03, 95%, confidence interval CI -0.05 to -0.01, P-value 0.01, Heterogeneity I^2 =4%). (Figure 3.2)

Figure 3.2 Wound complications including infections forest plot analysis. The black diamond signifies that the mean difference is in favour of TXA. The size of each square depends on the weight of each study as detailed in the forest plot. A green coloured square is given to continuous outcomes and a blue square to dichotomous outcomes.



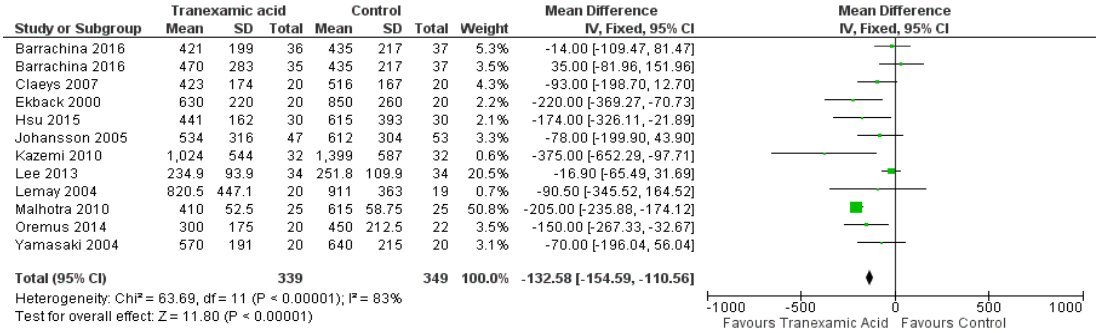
3.3.2.2 Blood Loss:

3.3.2.2.1 Intraoperative Blood Loss

Eleven studies (Ekback et al., 2000, Claeys et al., 2007, Lemay et al., 2004, Johansson et al., 2005, Yamasaki et al., 2004, Barrachina et al., 2016, Hsu et al., 2015, Kazemi et

al., 2010, Lee et al., 2013, Malhotra et al., 2010, Oremus et al., 2014) with a total of 688 patients were eligible for this outcome. Using TXA significantly reduced intraoperative blood loss as measured by weighing sponges and suction drainage by an average of 132.58 ml (95%CI -154.59 to -110.56, P <0.01). However, there was significant heterogeneity among the studies included (I^2 =83%). (Figure 3.3)

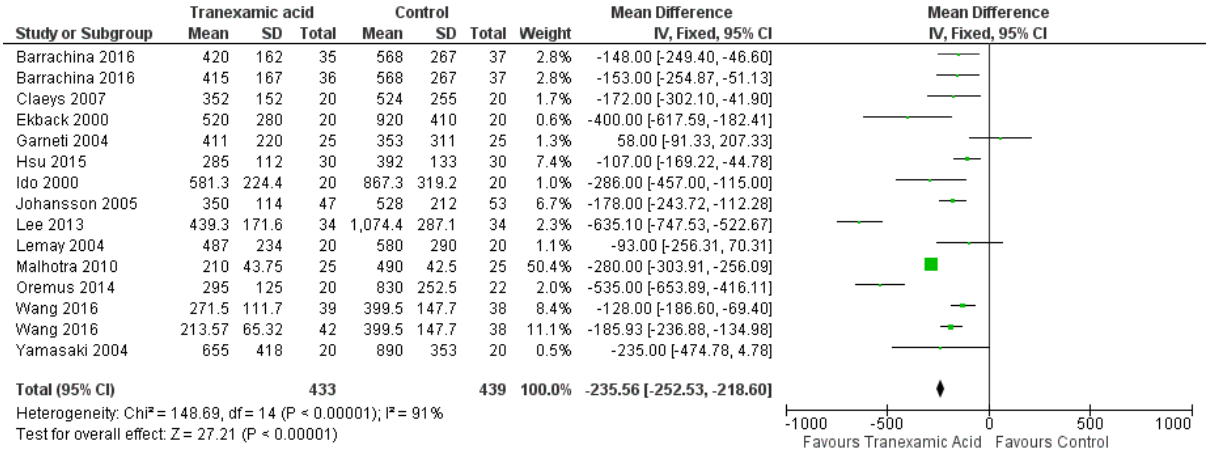
Figure 3.3 Intraoperative Blood Loss Forest Plot Analysis



3.3.2.2.2 Postoperative Blood Loss

Thirteen studies (Yamasaki et al., 2004, Ekback et al., 2000, Ido et al., 2000, Johansson et al., 2005, Claeys et al., 2007, Lemay et al., 2004, Garneti and Field, 2004, Barrachina et al., 2016, Hsu et al., 2015, Lee et al., 2013, Malhotra et al., 2010, Oremus et al., 2014, Wang et al., 2016) including 872 patients were eligible for this outcome. Using TXA significantly reduced postoperative blood loss as measured by drain volume by an average of 235.56 ml (95%CI -252.53 to -281.60, P-value <0.01). However, there was significant heterogeneity among the studies included (I^2 =91%). (Figure 3.4)

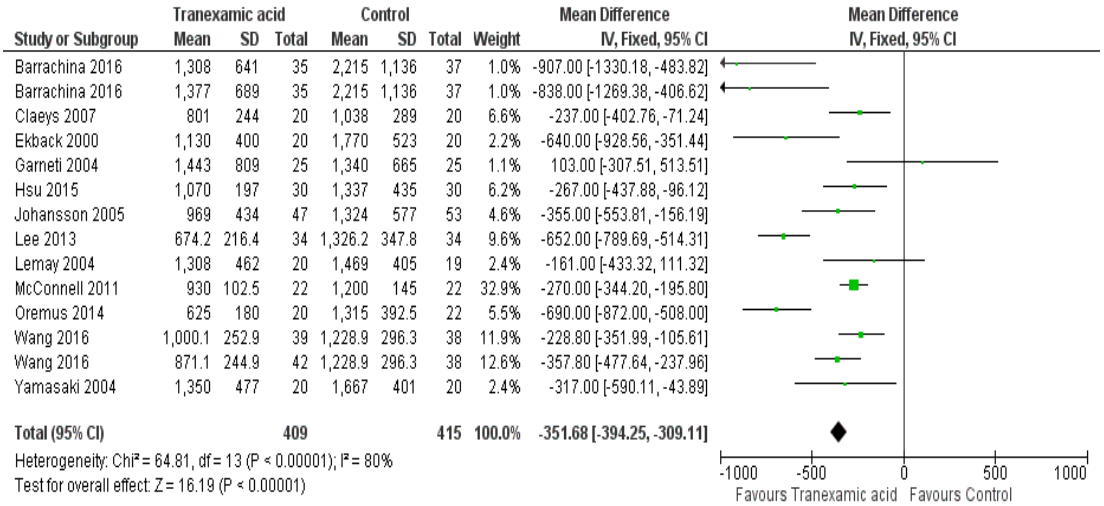
Figure 3.4 Postoperative Blood Loss Forest Plot Analysis



3.3.2.2.3 Total Blood Loss

TXA had a similar effect on total blood loss as it significantly reduced it by an average of 351.68 ml (95%CI -394.25 to -309.11, P< 0.01). However, again there was significant heterogeneity (I^2 =80%) among the studies included (Garneti and Field, 2004, Ekback et al., 2000, Johansson et al., 2005, Yamasaki et al., 2004, Claeys et al., 2007, Lemay et al., 2004, Barrachina et al., 2016, Hsu et al., 2015, Lee et al., 2013, McConnell et al., 2011, Oremus et al., 2014, Wang et al., 2016). (Figure 3.5)

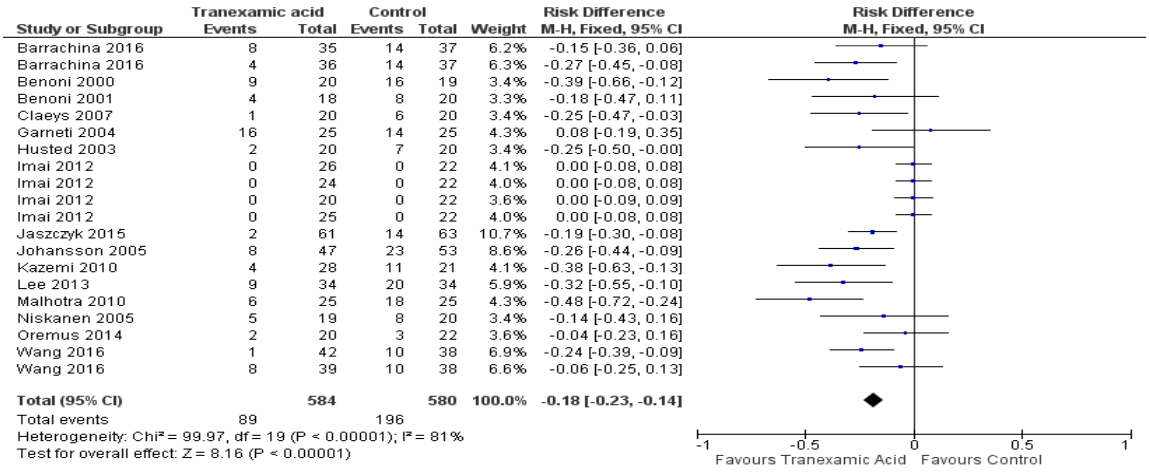
Figure 3.5 Total Blood Loss Forest Plot Analysis



3.3.2.3 Blood transfusion

Fifteen studies (Benoni et al., 2001, Benoni et al., 2000, Johansson et al., 2005, Claeys et al., 2007, Husted et al., 2003, Niskanen and Korkala, 2005, Garneti and Field, 2004, Barrachina et al., 2016, Imai et al., 2012, Jaszczyk et al., 2015, Kazemi et al., 2010, Lee et al., 2013, Malhotra et al., 2010, Oremus et al., 2014, Wang et al., 2016) with a total of 1164 patients. TXA led to an 18% reduction in blood transfusion requirements (RD -0.18, 95%CI -0.23 to -0.14, P-value <0.01, I^2 =81%). (Figure 3.6)

Figure 3.6 Blood Transfusion Forest Plot Analysis



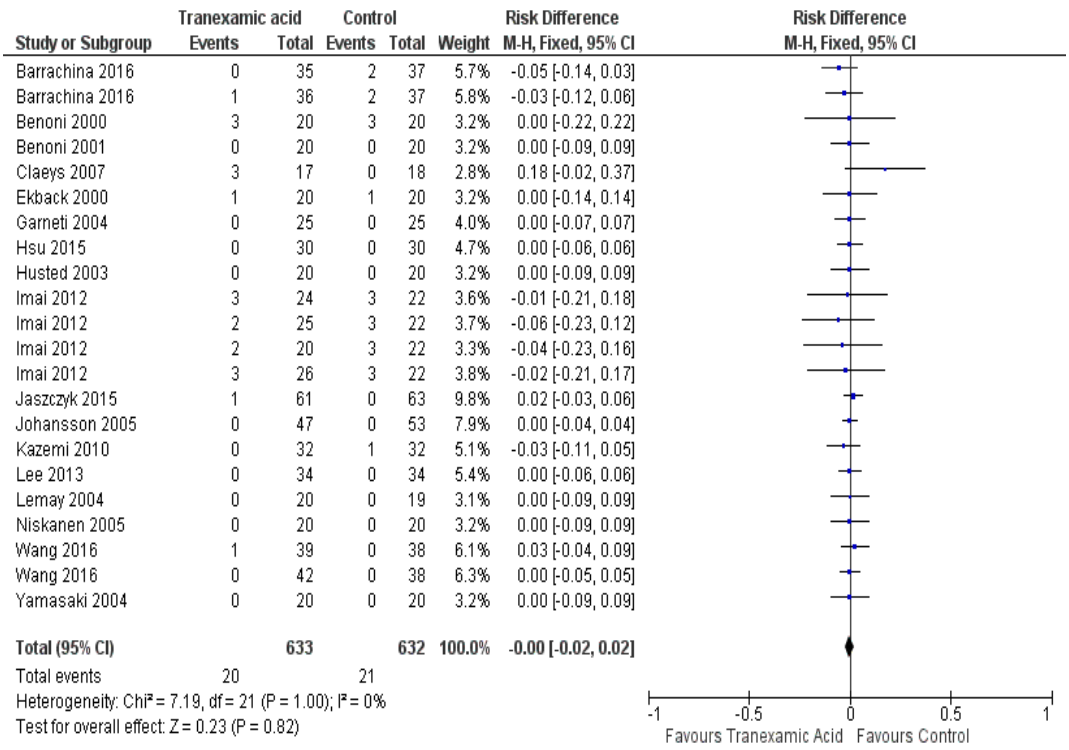
3.3.2.4 Complications:

3.3.2.4.1 Deep Vein Thrombosis

Sixteen trials (Garneti and Field, 2004, Johansson et al., 2005, Husted et al., 2003, Benoni et al., 2000, Benoni et al., 2001, Ekback et al., 2000, Lemay et al., 2004, Niskanen and Korkala, 2005, Yamasaki et al., 2004, Claeys et al., 2007, Barrachina et al., 2016, Hsu et al., 2015, Imai et al., 2012, Jaszczyk et al., 2015, Kazemi et al., 2010, Lee et al., 2013, Wang et al., 2016) reported on DVT with a total number of 1265 patients of whom 633 received TXA. There was no significant difference among the

study groups in relation to a higher risk of developing DVTs (P-value 0.82). (Figure 3.7)

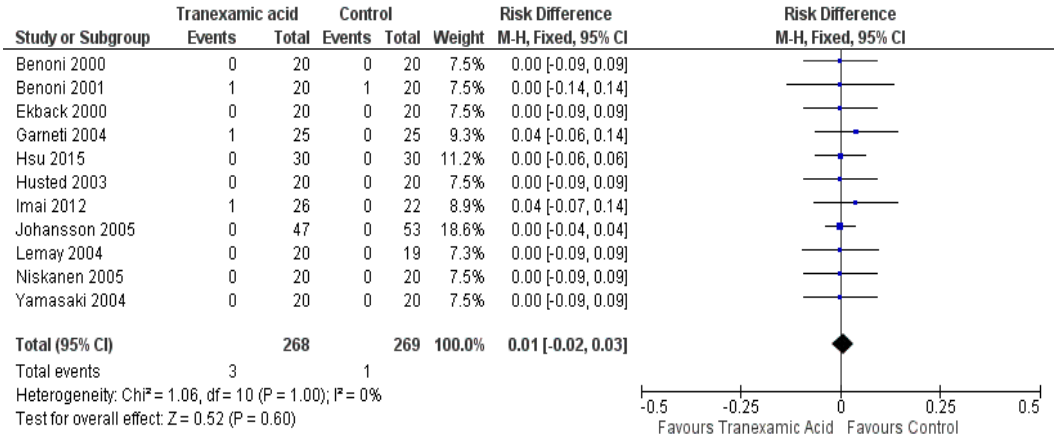
Figure 3.7 DVT Forest Plot Analysis



3.3.2.4.2 Pulmonary Embolism

There were four reported events of PE in the 21 trials we studied (Benoni et al., 2001, Garneti and Field, 2004, Imai et al., 2012); three in the TXA group and one in the control group. However, there was no statistical significance in the risk of developing among the groups (P-value 0.60). (Figure 3.8)

Figure 3.8 PEs Forest Plot Analysis

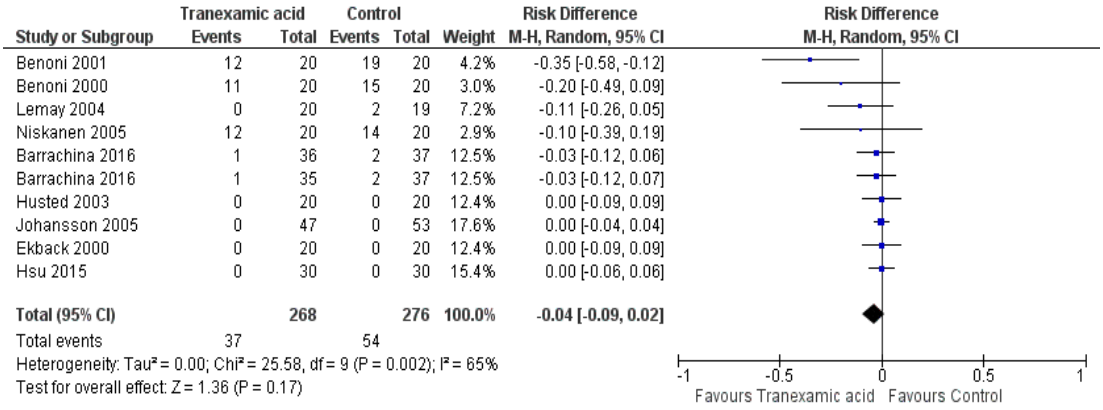


3.3.2.4.3 Other Complications

In this section, we compared all other reported adverse events among the groups. Systematic complications reported included one case of a brief respiratory arrest related to delay in volume replacement from early postoperative blood losses treated with no complications (Lemay et al., 2004), a case of delirium in the postoperative period from unrecognised alcohol withdrawal necessitating re-intubation in the post anesthesia care unit (Lemay et al., 2004), a patient who went into urinary retention and was treated with a suprapubic catheter (Niskanen and Korkala, 2005), a patient who had transient chest discomfort and fever 4 weeks after the operation which settled spontaneously (Benoni et al., 2000), a patient who had nausea on administration of the drug (Benoni et al., 2001) and a case of lower limb oedema and a viral infection in the control group (Barrachina et al., 2016). In the TXA group, a patient developed transient dyspnoea on the third postoperative day (Niskanen and Korkala, 2005), a patient had pyelonephritis one month after the operation (Niskanen and Korkala, 2005), a patient developed pulmonary oedema and another gastroenteritis (Barrachina et al., 2016) and one patient developed slight hemiparesis 58 days postoperatively but a CT scan of her brain was normal. A CT scan performed 3 months later, after another

episode, showed signs of older infarctions in the right hemisphere (Benoni et al., 2001). Overall, the results showed that using TXA was associated with fewer such complications. However, this did not reach a statistically significant level (P=0.17). (Figure 3.9)

Figure 3.9 Other Complications Forest Plot Analysis



3.4 Discussion

There are several issues related to quality control in conducting a meta-analysis; particularly study selection and homogeneity of these studies. A systematic review and meta-analysis with homogeneity is regarded as level Ia evidence. Hence, this study focused on the use of intravenous TXA in THA as a single group to reduce heterogeneity related to other routes of tranexamic application, other antifibrinolytic agents and other types of surgeries.

The most significant result of this meta-analysis is the consistency of TXA in reducing wound complications after primary THAs with no heterogeneity in the studies included. The effect of TXA on wound healing has never been analysed in meta-analyses of RCTs previously which could be an important addition to the advantages of using TXA in hip replacement surgery. Similarly, TXA reduced blood loss and allogeneic blood transfusion requirements. However, there has been significant heterogeneity among the studies evaluating these outcomes. Despite our best efforts to produce comparable outcomes, variations which may have accounted for such heterogeneity include the following:

1. The difference in sample sizes
2. The variation of patients' demographics such as age and severity of the underlying illness
3. Inclusion and exclusion criteria for each study
4. The differences in management protocols and logistics between treating centres including surgical technique and procedure, type of anaesthesia, TXA doses, the time and mode of administration, blood transfusion trigger and DVT prophylaxis
5. Different strategies for measuring the outcomes. For example, postoperative blood loss was measured at 12, 24, 36 and 48 hours postoperatively according to the study performed.

Two studies included in the meta-analysis did not support the routine use of TXA in THA in relation to blood loss and transfusion requirements. Benoni 2000 (Benoni et al., 2000) performed a randomised double-blinded RCT on 39 THAs where TXA was given at the end of the operation and 3 hours later in 20 patients and an equivalent protocol of normal saline was given to 19 patients. Results showed that TXA did not significantly reduce intra or postoperative blood loss (550ml vs. 500ml and 440ml vs. 450ml respectively). However, both the authors of the study and results of our meta-analysis relate these findings to the fact that TXA was given too late to show a significant effect as most of the other studies delivered TXA preoperatively with overall good results. Additionally, this study reported higher wound complications (9 vs. 16) as well as overall complications (11 vs. 15) in the control group. Garneti et al (Garneti and Field, 2004), on the other hand, randomised 50 patients to receive either a single dose of TXA or a similar volume of saline as a preoperative bolus. Results were in favour of the placebo group with a mean postoperative blood loss of 353ml (+/-311) vs. 411ml (+/-220) for the TXA group and 1340ml (+/-665) vs. 1443ml (+/-809) total blood loss for each group respectively. Reasons for these discrepancies from other study results are unclear. Patient numbers, surgical time, dose, duration, time of administration of the drug in relation to the surgery, and number of times the drug was administered were proposed as possible contributing factors by the authors. Additionally, a greater number of patients in the TXA group required transfusion than in the placebo group; 64% (16 of 25) of patients in the TXA group required transfusion compared with 56% (14 of 25) in the placebo group. However, this was attributed to the different transfusion strategies of the anaesthetists, one of whom transfused most patients unless they were young and healthy and the fact that there was no defined transfusion protocol which could have been a source of bias.

There are other meta-analyses which studied the relationship between TXA and blood loss and/or transfusion after THA but none evaluated wound complications as the primary

outcome of interest. Zufferey (Zufferey et al., 2006) analysed the effect of intravenous antifibrinolytics including TXA, aprotinin and EACA on blood transfusion in surgeries including primary hip and knee arthroplasties, major orthopaedic procedures including revision or bilateral arthroplasty, spinal fusion or posterior spinal fixation, musculoskeletal sepsis and tumours. Only studies with a transfusion protocol were analysed which resulted in 5 studies of TXA being included for the blood transfusion outcome. Results on blood transfusion were similar to our study with an overall favourable outcome using TXA especially when considering a multiple doses regimen. However, TXA effect on blood loss was briefly discussed as part of 'other efficacy endpoints' and was evaluated as a single group under 'perioperative blood loss' with no clear definition of the blood loss.

Kagoma (Kagoma et al., 2009), (Gill and Rosenstein, 2006) (Huang et al., 2015) also reviewed the evidence of using TXA, EACA and aprotinin on total blood loss and transfusion rates in total knee and hip arthroplasties. Despite similar trends in blood conservation, all three antifibrinolytics were either analysed as a single group or the effects of each of them evaluated for both hip and knee arthroplasties.

Ho and Ismail (Ho and Ismail, 2003) studied the effect of TXA in reducing blood transfusion after total hip and knee arthroplasties. However, most of the studies were on knee arthroplasties with only 4 studies relating to THA and 3 suitable for measuring blood transfusion rates. Blood loss was again collectively defined as 'perioperative blood loss' despite including results of total blood loss as well as postoperative blood loss under this definition when studies were analysed. There was no significant increase in risk of thromboembolic events associated with TXA in either study which agrees with our conclusions. Similar findings were reported by Wei (Wei and Liu, 2015), Khan (Khan et al., 2015) and Gandhi (Gandhi et al., 2013) but again the authors collectively analysed patients

who underwent THA and TKA and Wei (Wei and Liu, 2015) and Khan (Khan et al., 2015) also included all routes (oral, IV and topical) of TXA application in their analysis. Pinzon-Florez (Pinzon-Florez et al., 2015) in a recent meta-analysis reported on TXA effect in reducing blood loss and transfusion rates after THA surgery. Whilst reduction in blood loss outcome showed significant results, the trends in lowering transfusion rates did not. Zhou (Zhou et al., 2013) also analysed the effect of IV TXA in reducing blood loss and transfusion rates in THA. Despite an overall reduction of blood loss and transfusion rates, they included studies which are not RCTs (Rajesparan et al., 2009, Singh et al., 2010, Clave et al., 2012) which was also noted in a number of the above meta-analyses as well.

There are several strengths of this meta-analysis. First, we conducted a thorough literature search of RCTs, including publications in any language as well as unpublished abstracts. Second, the QAS was high for most of the studies included which contributes to the strength of point estimates and conclusions drawn from the meta-analysis. Third, the meta-analysis showed favourable outcomes when using TXA in reducing wound complication rates with no significant heterogeneity among the studies or an increased risk of thromboembolic events. Fourth, cost-effectiveness analyses in four studies were all in favour of using TXA over blood transfusion products.

Limitations of this meta-analysis included the lack of comparison between TXA and other blood conservation methods such as using erythropoietin and preoperative autologous blood donation and postoperative autotransfusion. Additionally, trials included in our study were designed to assess the efficacy and safety of TXA in primary THA where an exclusion of high risk patients with history of cardiovascular disease and previous thromboembolic events was the case in most of the studies included. Therefore, no definite conclusions regarding TXA safety can be derived from our meta-analysis in relation to revision hip arthroplasty or

in high risk patients. There has not been enough data also to support the analysis of functional outcome scores or quality of life outcome measures as planned originally for our secondary outcomes.

3.5 Conclusion

In summary, we conclude that TXA significantly reduced wound complication rates after primary THA with no significant increase in complication rates. Favourable results have also been suggested for the blood loss and transfusion rate outcomes but with significant heterogeneity which necessitates careful interpretation of TXA effect in this context. Additionally, future randomised trials of sufficient power should be designed to examine the efficacy and safety of TXA in revision hip surgery and its efficacy in comparison to other blood conservation methods.

Chapter 4

Is Single-stage Revision According to a Strict Protocol Effective in Treatment of Chronic Knee Arthroplasty Infections?

4.1 Introduction

Most TKA studies today report infection in fewer than 2% of primary and 5% of revision procedures (Moran et al., 2007, Laffer et al., 2006, Tintle et al., 2009, Vanhegan et al., 2012b). Nevertheless, both diagnosis and management of periprosthetic TKA infections remain challenging because the ability to detect and eradicate pathogens in periarticular structures and the magnitude of the host response to infection vary with the virulence of the infecting organism and the immunocompetence of the host (Haddad et al., 2000a). Management depends on a number of factors including the acuteness or chronicity of the infection, the infecting organism and its sensitivity profile to antibiotics, the health of the patient, the fixation of the prosthesis, available bone stock, and the particular philosophy and training of the surgeon (Haddad et al., 2000a, Zimmerli and Ochsner, 2003, Oussedik et al., 2012).

Two-stage revision remains the standard for treatment of chronic TKA infections because many series report the successful eradication of a PJI in more than 90% of patients using this approach (Zimmerli et al., 2004, Haddad et al., 2000a, Laffer et al., 2006). Furthermore, it permits the use of allografts, which is particularly important given the frequency of femoral and tibial defects associated with TKA infections (Haddad et al., 2000b, Lai et al., 1996). Nevertheless, this procedure is costly, time-consuming, and may result in increased damage to bone and surrounding soft tissues (Vanhegan et al., 2012b).

Single-stage revision in selected cases has become an appealing alternative because it involves only one surgical procedure and, if comparably effective, will be associated with less patient morbidity and potentially improved functional outcomes and less expense (Oussedik et al., 2010, Gulhane et al., 2012, Vanhegan et al., 2012b). Eradication of infection using a single-stage strategy in selected patients is achieved in 67% to 95% of patients

(Buechel et al., 2004, Goksan and Freeman, 1992, Silva et al., 2002, Singer et al., 2012, Lu et al., 1997, Sofer et al., 2005, von Foerster et al., 1991).

At our institution, we carry out single-stage TKA revisions for chronic infections in very selected circumstances and, therefore, we determined in this study (1) the degree to which our protocol of a highly selective single-stage revision approach achieved infection-free survival compared with a two-stage revision approach to TKA infections; and (2) Knee Society scores and radiographic evidence of implant fixation between the single-stage and two-stage patients who were treated for more complicated infections.

4.2 Patients and Methods

We performed a retrospective cohort analysis of a prospectively compiled register of all 102 patients diagnosed with chronic infected TKAs of whom 28 (27%) were treated using a single-stage approach and 74 (73%) were treated using a two-stage approach between 2004 and 2009. All patients were available for follow-up at a minimum of 3 years (mean, 6.5 years; range, 3-9 years).

In the two-stage revision group, 12 patients had undergone two and 24 undergone one previous aseptic revision. There were no prior revision procedures in the remaining 38 patients. In the single-stage group, eight patients had undergone aseptic revisions and the rest were primaries.

At our institution, a patient with suspected TKA infection is promptly referred to the knee surgeons who deal with PJIs regularly because this is a specialised procedure and there is no role for simple incision and drainage or repetitive washouts, which result in emergence of resistant microorganisms (Vanhegan et al., 2012b). Clinical presentation (pain, fever, swelling, skin redness, discharging sinus), serologic testing (erythrocyte sedimentation rate [ESR] > 30 mm/hour; C-reactive protein [CRP] > 10 mg/L), knee aspiration, and biopsy samples help us diagnose PJI (Sukeik and Haddad, 2009c, Vanhegan et al., 2012b). Definitive diagnosis, however, is established when three to six specimens are sampled from different sites at the time of surgery (e.g., capsule, femur and tibia) and the same microorganism is cultured from at least three specimens (Zimmerli and Ochsner, 2003, Atkins et al., 1998, Vanhegan et al., 2012b).

A decision to perform surgery was based on either growing a microorganism from the tissue aspiration/biopsies or presence of a sinus tract communicating with the prosthesis. A microorganism was identified preoperatively in all single-stage patients and in 65 of the two-

stage patients, whereas the remaining nine patients were identified postoperatively only despite the presence of a discharging sinus in five patients. The remaining four patients had compelling evidence of PJI with elevated inflammatory markers, loose prostheses, and purulence on aspiration of the joints despite the absence of an isolated microorganism.
We graded all patients according to a standardised protocol for chronic hip and knee PJIs based on the criteria previously set out by Haddad (Haddad et al., 1999) and considered them for either a single- or two-stage revision procedure accordingly. The indications for using a single-stage approach during the period in question included (1) insignificant bone loss (e.g. Anderson Type III defects (Engh and Ammeen, 1999, Engh and Parks, 1997)] or a soft tissue defect that could be closed primarily; (2) non-immunosuppressed hosts: patients who are not rheumatoid or diabetic or on immunosuppressant medication and did not have ongoing sepsis elsewhere or chronic disease such as anaemia or cancer; and (3) isolation of a single low virulent organism preoperatively, which is sensitive to bactericidal antibiotic treatment. Hence, we excluded polymicrobial infections and multi-resistant organisms such as *MRSA* and *MRSE* and included appropriate patients only after discussion with our microbiologist colleagues. If patients had any of the contraindications, they underwent a two-stage revision instead.

There were 28 patients in the single-stage group with a mean age of 63 years (range, 48-87 years) and equal distribution of 14 women and men. On the other hand, the two-stage group included 74 patients with a mean age of 68 years (range, 45-85 years) 41 of them were women and 33 were men. Overall there were 12 patients with sinus tracts communicating with the prosthesis all in the two-stage group. No bilateral infections were included in our study. No patient had a history of infection of the affected knee. The majority of patients had osteoarthritis as the underlying pathology for their primary TKA (74 patients) followed by

inflammatory arthropathy (20 patients) and posttraumatic/acute vascular necrosis resulting in secondary osteoarthritis in eight patients. In patients who had undergone revision TKA, the original indications for reoperation after their primary procedures were aseptic loosening and wear. Comorbidities were assessed according to the American Society of Anaesthesiologists (ASA) grading system (Little, 1995); nine patients were Grade I, 56 Grade II, and 37 Grade III. Three patients died during the follow-up period but had a minimum of 2 years' data available for analysis. No patients were recalled specifically for this study; all data were obtained from medical records and radiographs.

4.3 Surgical Technique: Single-stage Revision

The operation consists of open aggressive débridement with removal of all components and cement, during which multiple samples are sent to microbiology before administration of antibiotics and the knee is irrigated with hydrogen peroxide and Betadine® solutions (Videne, Ecolab Ltd, Swindon, UK) and pulsatile lavage. The wound is then soaked in aqueous Betadine® and the wound edges are approximated. The patient is then re-draped, the surgical team rescrubs, and new instruments are used. After a further lavage, implantation of a new prosthesis is performed using ALC according to known sensitivities at a volume of < 5% of the total weight of cement powder. For example, we commonly used 1 g vancomycin and 1 g gentamicin per 40-g bag of Palacos®*R (Heraeus Medical, Wehrheim, Germany)* for our single-stage revisions. Postoperatively, patients continue antibiotic therapy tailored to the sensitivities of intraoperative cultures for at least 6 weeks until inflammatory markers (CRP, ESR) and nutritional markers such as plasma albumin concentration return to stable limits (levels normalised in 90% of cases). Normal levels were defined as an ESR < 30 mm/hour, CRP < 10 mg/L, and albumin 35 to 50 g/L. The change from intravenous to oral therapy is effected as soon as we have a full organism sensitivity profile and after consultation with our

infectious diseases team with whom we have a fortnightly multidisciplinary meeting (IV antibiotics for 1 week: four patients, 2 weeks: seven patients, 6 weeks: 17 patients). Long-term oral suppressive antibiotic therapy was not used in any patients after IV treatment had concluded.

4.4 Surgical Technique: Two-stage Revision

Intraoperatively, the first part of the operation is similar to a single-stage revision. However, after rescrubbing and re-draping, a temporary articulating ALC spacer is implanted instead. This spacer normally contains 3 g vancomycin and 2 g gentamicin per sachet of Palacos®*R (Heraeus Medical)*, which provides a broad spectrum of coverage for organisms commonly encountered with deep periprosthetic infections while reducing the development of resistant strains (Anagnostakos et al., 2006). Postoperatively, the patient is allowed to mobilise partial weightbearing with crutches and is discharged home when deemed safe. All patients had IV antibiotics for the first 5 days and then either IV or oral antibiotic therapy was continued and tailored to the sensitivities of intraoperative cultures and continued for 6 weeks (seven patients had 2 weeks of IV and then oral antibiotics, five had 6 weeks of IV antibiotics). The decision to proceed with insertion of a new prosthesis is determined by the clinical response of the patient including wound healing and inflammatory and nutritional markers indicating resolution of infection, which is confirmed after 2 weeks of discontinuing any antibiotics the patient was taking and performing a further aspiration which came back as negative for infection. At the second stage, the spacer is removed and the underlying cement mantle is fragmented and removed piecemeal without sacrificing bone stock. An appropriate prosthesis is then reimplanted with cemented components, and allografts may be used in cases of severe bone loss. Types of implants and augments used are listed (Table 4.1).

Table 4.1 Types of implants/reconstructions used for the single and two-stage revisions of infected TKAs

	Single-stage	Two-stage
Augments	4	9
Cones	2	5
Stems on one side or both	28	74
Semi-Constrained Implants	18	50
Hinges	7	19
Bone Graft	0	6

Regardless of the treatment strategy followed, we review all our patients postoperatively at 6 weeks, 6 months, 1 year, and then on a yearly basis looking for clinical symptoms and signs of infection as well as CRP and ESR. Professor Haddad performed all the procedures. We obtain plain radiographs including AP, lateral, and skyline views of both knees at every follow-up appointment. We assess component position, radiolucencies/osteolysis, and loosening according to the American Knee Society recommendations (Ewald, 1989 , Sarmah et al., 2012). Distinguishing infective loosening from aseptic loosening radiographically can be difficult; however, signs of an infected knee arthroplasty include progressively enlarging lucencies, endosteal scalloping, periostitis, and focal lysis (Sarmah et al., 2012)]

Eradication of infection is defined as absence of clinical, serologic, and radiographic signs of infection and absence of death secondary to infection or treatment during the follow-up period. We used the MSIS criteria in our last outpatient review to assess and confirm eradication of infection (Parvizi et al., 2011b). We define failure as any major operation performed in any subgroup of patients for eradication of infection, including a two-stage revision, excision arthroplasty, arthrodesis, and amputation, or the need for long-term antibiotic suppression. We consider reinfection to be an infection with the same or another

organism. The mean interval time between each stage was 62 days (range, 42-119 days). Duration of antibiotic treatment was 63 days (range, 42-85 days) for the single-stage group and 12 days (range, 5-42 days) for the two-stage group.

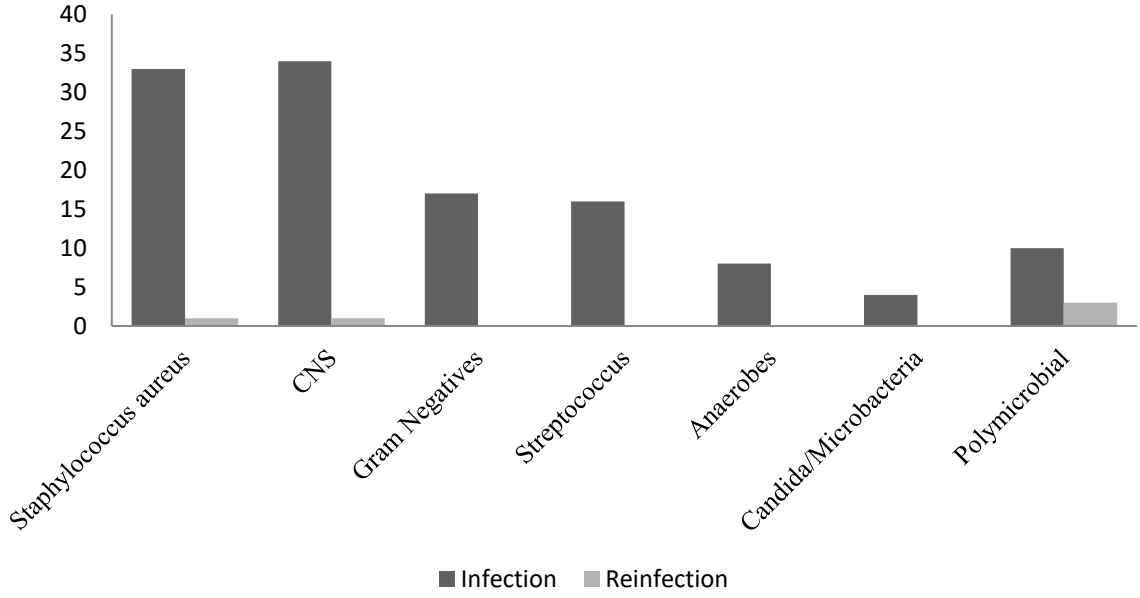
The causative microorganism was identified preoperatively in all single-stage patients and in 65 of the two-stage patients, whereas the remaining nine patients were identified postoperatively. Microbiology from intraoperative tissue sampling confirmed bacterial infection in all patients with the most commonly isolated organism being coagulase negative *Staphylococcus* (34 patients [33%]) of which nine were methicillin-resistant followed by *S aureus* (33 patients [32%]), of which 11 were methicillin-resistant (Table 4.2).

Table 4.2 Microorganisms grown from intraoperative tissue biopsies

Microorganism	Single- stage	Two-stage
Staphylococcus aureus	8	25
(methicillin-resistant *S aureus*)	(0)	(11)
Coagulase-negative *Staphylococcus*	11	23
(methicillin-resistant *Staphylococcus epidermidis*)	(0)	(9)
Streptococcus	4	12
Gram-negatives	4	13
Anaerobes	1	7
Candida/Mycobacterium tuberculosis	0	4
Polymicrobial	0	10

Other microorganisms isolated included Gram-negatives (17 patients), *Streptococcus* (16 patients), anaerobes (eight patients), *Candida* (three patients) and *Mycobacterium tuberculosis* (one patient). Ten patients had polymicrobial infections. Most common reinfections were the result of polymicrobial infections (Fig. 4.1).

Figure 4.1 Micro-organisms responsible for infections and re-infections, CNS: Coagulase Negative Staphylococcus



The functional outcome for all patients was evaluated using the Knee Society scoring system, which was recorded preoperatively and at the 2-year follow-up.

Statistical analysis was carried out using the two-sample t-test or Mann-Whitney U-test for continuous outcomes and a chi square test or Fisher's exact test for categorical outcomes.

4.5 Results

None of the patients in the single-stage revision group developed recurrence of infection, and five patients (7%) in the two-stage revision group developed reinfection ($p = 0.16$). Those patients, however, underwent a further two-stage revision procedure and had their infections eradicated at last follow-up.

The Knee Society score was higher in the single-stage group at 2 years than in the two-stage group (mean 88 (range 38-97) versus 76 (range 29-93, $p < 0.001$). Both groups improved in this score after successful reconstruction from a mean of 32 (range 18-65) to a mean of 88 (range 38-97) in the single-stage group and 31 (range 17-70) to 76 (range 29-93) in the two-

stage group (Table 4.3). Radiographic findings showed a well-fixed prosthesis in all patients of both groups with no evidence of loosening at the most recent follow-up.

Table 4.3 Knee Society scores and visual analogue scale satisfaction scores

Outcomes	Single-stage	Two-stage	p value
Number of patients	28	74	N/A
Recurrent infection	0	5	< 0.01
KSS preoperatively	32 (18-65)	31 (17-70)	NS
KSS at 2 years	88 (38-97)	76 (29-93)	< 0.02
Difference in KSS	56	45	< 0.02
Visual analogue scale at 2 years	7.82	6.18	< 0.01

Ranges in parentheses; KSS = Knee Society score; N/A = not applicable; NS = not significant.

4.6 Discussion

Despite the relatively low rates of PJIs after TKAs, they remain a leading cause of revision surgery as a result of an ever increasing number of knee arthroplasties performed yearly for an aging population (Vanhegan et al., 2012b, Haddad et al., 2000a). In contrast to two-stage revisions, single-stage surgery may offer a shorter hospital stay, the avoidance of complications associated with a second operation, improved postoperative function and pain, and lower cost; however, whether eradication of infection is sacrificed for these endpoints remains controversial, and if it is, a single-stage approach would likely not be justified. In this study, we therefore determined (1) the degree to which our protocol of a highly selective single-stage revision approach achieved eradication of infection compared with a two-stage revision approach to TKA infections; and (2) Knee Society scores and radiographic evidence of implant fixation between the single-stage and two-stage patients who were treated for more complicated infections.

Our study is associated with some limitations. First, a single-stage revision procedure was applied in a highly selected patient population using the indications we have defined (Table 4.1) and is not suitable for all chronic infections. Second, patients undergoing two-stage procedures tend to have been more complicated taking into consideration that they had undergone multiple revision procedures, and had less bone stock to start off with, which may account for the more complex reconstructions and the higher observed Knee Society scores in the single-stage patients. Third, eradication of infection after knee arthroplasties can be affected by a number of risk factors, including age, sex, time from operation, duration of symptoms, patient comorbidities, and the pathogen causing the infection (Della Valle et al., 2004, Haddad et al., 2000a, Vanhegan et al., 2012b). Because of the small number of patients within each subgroup, the heterogeneity of the study population and the retrospective nature of this study with some data occasionally missing such as the type of implants used in the

primary operations, number of previous revisions, comorbidities and risk factors for infection, we were unable to perform a multivariate analysis to further investigate the effect of those risk factors on eradication of infection. Fifth, despite no recurrence of infection in the single-stage group of patients, the numbers included in this study remain small. This, however, reflects the difficulty of finding large numbers suitable for a single-stage revision even at a tertiary center dealing with significant numbers of periprosthetic infections.

Our results for eradicating infection using two-stage revision for chronic infections are consistent with those previously reported in the literature, especially where a clear protocol has been followed (Laffer et al., 2006, Meek et al., 2003, Haddad et al., 2000a, Zimmerli et al., 2004, Leone and Hanssen, 2005, Pitto et al., 2005, Barrack et al., 2000, Freeman et al., 2007, Haleem et al., 2004). It is of note, however, that the inclusion and exclusion criteria as well as management protocols and definition of infection varied among those studies, occasionally including all four types of periprosthetic infections rather than chronic infections only. Additionally, some of the studies did not differentiate between knees and hips when reporting their results, which resulted in a wide range of infection-free survival. On the other hand, single-stage revisions for chronic infections are regaining momentum and our results certainly reflect a strict protocol, which has led to infection-free survival in all cases selected for single-stage revision (Buechel et al., 2004, Goksan and Freeman, 1992, Lu et al., 1997, Silva et al., 2002, Singer et al., 2012, Sofer et al., 2005, von Foerster et al., 1991). (Table 4.4)

Table 4.4 Previous studies reporting infection eradication after single-stage revision for infected TKAs

Study	Number of cases	Infection eradication %	Follow-up (years)
Buechel et al, 2004 [4]	22	90.9	10.2
Goksan and Freeman, 1992 [10]	18	88.8	5
Lu et al, 1997 [20]	8	87.5	1.7
Silva et al, 2002 [30]	37	89.2	4
Singer et al, 2012 [31]	63	95	3
Sofer et al, 2005 [32]	15	93	1.5
von Foerster et al, 1991 [36]	104	73.1	6.3

The only study with equivalent results to our study reporting 100% infection-free survival with a single-stage strategy was recently published by Parkinson (Parkinson et al., 2011). However, in their 12-patient series, they did not mention details about the inclusion criteria for their protocol apart from growing a microorganism from the arthroscopy performed preoperatively for a diagnosis of infection. Additionally, there are no details regarding the type of infection treated (acute or chronic, postoperative or hematogenous).

Other studies also reported improvement in Knee Society scores after a single-stage revision for PJI. For example, Singer (Singer et al., 2012) reported a mean Knee Society score of 72 points after 24 months and a mean reported range of movement of 104°. Buechel (Buechel et al., 2004) also had a similar mean final postoperative knee score of 79.5 (range, 35–94). This may support an easier convalescence as a potential advantage of a single-stage procedure, especially with no differences found in prosthesis fixation as seen in our current study at the latest follow up.

4.7 Conclusion

In conclusion, our data suggests that single-stage revision surgery in chronic TKA infections achieve a high rate of infection-free survival when patients are carefully selected. However, larger, multicenter, prospective trials are called for to validate our findings.

Chapter 5

PJI after THA: The Ten Year Outcomes of an Algorithmic Approach

5.1 Introduction

Health services are experiencing an exponential global rise in numbers of lower limb arthroplasty procedures performed for an ageing population. Over the last 5 years, the UK National Health Service witnessed a growth of hip and knee arthroplasty procedures by 4000–5000 cases/year (NJR, 2011). Subsequently, even a minimal prosthetic joint infection (PJI) rate of 0.57% constitutes a major concern (Phillips et al., 2006) especially with the financial burden of a single revision procedure for sepsis exceeding £21,000 (Vanhegan et al., 2012a). The picture is further complicated by the continuous metamorphosis and emergence of new resistant bacterial strains as well as infections with rare organisms (Chodos and Johnson, 2009, Eid et al., 2007).

Challenges including diagnostic uncertainty, immunocompromised patients, recurrent infection, infection around a well-fixed implant and substantial bone loss require careful preoperative assessment and well defined treatment plans (Haddad et al., 1999). However, until recently there has been no consensus over a standard treatment strategy for PJIs which has accounted for the extensive variability in infection eradication rates in the literature (Kaltsas, 2004, Ahlberg et al., 1978, Antti-Poika et al., 1989, Canner et al., 1984, Crockarell et al., 1998, Poss et al., 1984, Tsukayama et al., 1996, Stinchfield et al., 1980, Giulieri et al., 2004, Moyad et al., 2008). Therefore, specialist tertiary centres dealing with such infections on a regular basis using a multidisciplinary approach and clearly defined protocols may improve infection rates and contribute to standardising management of PJI after THA.
Our protocol involves aggressive surgery removing all mobile and non ingrown parts and exchanging them at the same sitting for acute infection, and a selective single stage versus two stage strategy for established infections based on host, organism and local factors.

We determined in this study (1) the rate at which our protocol eradicated THA infections, (2) the most common microorganisms responsible for both infections and reinfections, and (3) the final treatment modality resulting in infection-free survival for each patient at the last follow-up.

5.2 Protocol

At our institution, in a case of suspected THA infection, the patient is promptly referred to the hip team who deal with PJIs regularly as this is a specialised procedure and there is no role for simple incision and drainage or repetitive washouts which result in emergence of resistant microorganisms (Haddad et al., 1999, Sukeik and Haddad, 2009c). Clinical presentation (pain, fever, swelling, skin redness, discharging sinus), serologic testing (erythrocyte sedimentation rate [ESR] > 30 mm/hour; C-reactive protein [CRP] > 10 mg/L), hip aspiration and biopsy samples help us diagnose PJI (Sukeik and Haddad, 2009c). Definitive diagnosis however, is established when three to six specimens are sampled from different sites at the time of surgery (e.g. capsule, femur and acetabulum) and the same microorganism is cultured from at least three specimens (Zimmerli and Ochsner, 2003, Sukeik and Haddad, 2009c, Atkins et al., 1998). The extent of infection and the interval for which it has been present play a role in the choice of treatment and the chances for successful eradication of infection as follows:

5.2.1 Acute Infection

We define it as an infection occurring within 6 weeks of the index operation (primary or revision) or of haematogenous spread from a confirmed source of infection elsewhere in a previously well functioning implant. In haematogenous infections, a full workup to establish the source of infection is undertaken preoperatively, including a comprehensive history of recent systemic infections or invasive procedures causing bacteremic seeding of the hip, and investigations performed include a throat swab, chest radiograph, and urine, stool, and blood cultures (Sukeik et al., 2012). Decision to perform surgery is based on a high index of suspicion from clinical presentation and serologic testing. However, we do not perform preoperative diagnostic aspiration and biopsies in acute infections as this not only delays surgical intervention but also carries variable sensitivity and specificity rates for diagnosing

infection (0.50–0.93 and 0.82–0.97, respectively (Spangehl et al., 1999, Kraemer et al., 1993, Lachiewicz et al., 1996). Treatment of acute infection is subdivided according to the type of prosthetic fixation of the original implant:

5.2.1.1 Cemented Prostheses

We perform an aggressive open débridement with exchange of mobile parts and retention of the implant in stable components with no evidence of immunosuppression, and overlying soft tissue and skin of good condition (Davis, 2005, Zimmerli et al., 2004). The aim of rapid intervention with thorough open débridement is to prevent the production of any biofilm by the infecting organism, paramount for successful treatment of infection (Moyad et al., 2008). Patients undergo an open complete synovectomy, multiple tissue sampling, exchange of femoral heads and acetabular inserts, débridement of all aspects of the joint, irrigation with hydrogen peroxide and Betadine® solutions, and then pulsatile lavage.

5.2.1.2 Cementless Prostheses

For acute haematogenous infections in previously well functioning and well fixed implants, we follow the same protocol for cemented prostheses as detailed above. However, in acute postoperative infections, once the debridement is complete and samples are sent, all drapes, gowns, gloves and equipment are changed to create a new, sterile environment. We then proceed to a direct exchange single-stage cementless THA as this represents an ideal opportunity to remove both the implant and its biofilm prior to ingrowth (Hansen et al., 2013).

For both treatment modalities, patients continue antibiotic therapy tailored to the sensitivities of intraoperative cultures for at least 6 weeks until inflammatory markers (CRP, ESR) and the plasma albumin concentration return to within normal limits. Early conversion to oral antibiotics is dictated by sensitivities and consultation with our microbiology team with whom we have a fortnightly multidisciplinary meeting.

5.2.2 Chronic infection

In chronic PJIs, our protocol includes careful assessment of local soft tissues, baseline CRP and ESR, and hip aspiration combined with tissue biopsy as this has shown improved sensitivity and accuracy for diagnosing infection after at least 4 weeks of discontinuing any antibiotic therapy (Meermans and Haddad, 2010). We also perform plain anteroposterior and lateral radiographs, with additional CT if deemed necessary for further acetabular assessment. Once diagnosis of PJI is suggested by clinical findings and investigations, all patients are graded by the standardised protocol based on the criteria previously set out by Haddad et al (Haddad et al., 1999) (Table 4.1) and accordingly are either considered for single or two-stage revision procedure.

5.2.2.1 Single Stage Revision

At our institution single-stage revision is carried out under strict conditions including: minimal/moderate bone loss, non-immunocompromised patients, healthy soft tissues, a known organism with known sensitivities and when appropriate antibiotics are available. The operation is split into two parts; the first consists of an open aggressive debridement with removal of all components and cement, during which multiple samples are sent to microbiology and irrigation with hydrogen peroxide and Betadine® solutions, and then pulsatile lavage is done. The area is then soaked in aqueous betadine and the wound edges approximated. This is considered to be the end of the first part of the operation and the patient is re-draped and new instruments are used. The surgical team rescrubs and put on new gowns. After a further lavage, implantation of a new prosthesis is performed using ALC or antibiotic loaded bone graft as needed. Patients continue antibiotic therapy tailored to the sensitivities of intraoperative cultures for at least 6 weeks until inflammatory markers (CRP, ESR) and the plasma albumin concentration return to within normal limits. The change from intravenous to oral therapy is effected as soon as we have a full organism sensitivity profile.

5.2.2.2 Two stage Revision

This is the gold standard for treatment of chronically infected and complex THA infections as the successful eradication of a PJI is over 90% (Haddad et al., 2000b, Sukeik and Haddad, 2009b, Bejon et al., 2010, Biring et al., 2009, Cooper and Della Valle, 2013).

Intraoperatively, the first part of the operation is similar to a single stage revision. However, after rescrubbing and re-draping, a temporary articulating ALC spacer is implanted instead. This spacer normally contains 3 g of vancomycin and 2 g of gentamicin per sachet of Palacos R which provides a broad spectrum of coverage for organisms commonly encountered with deep periprosthetic infections whilst reducing the development of resistant strains. (Anagnostakos et al., 2006) Postoperatively, the patient is allowed to mobilise partial weight-bearing with crutches and is discharged home when deemed safe. Antibiotic therapy tailored to the sensitivities of intraoperative cultures is continued for 4 to 6 weeks. The decision to proceed with insertion of a new prosthesis is determined by the clinical response of the patient including wound healing, inflammatory and nutritional markers indicating resolution of infection together with performing a further aspiration which is negative. At the second stage, the spacer is removed and the underlying cement mantle is fragmented and removed piecemeal, without sacrificing bone stock. Appropriate implants are then reimplanted with either cemented or cementless components, and allografts may be used in cases of severe bone loss.

Regardless of the treatment strategy followed, we review all our patients postoperatively at 2 and 6 weeks, 6 months, 1 year, and then on a yearly basis, looking for clinical symptoms and signs of infection, as well as CRP and ESR level testing. We obtain plain radiographs including an AP pelvis and lateral of both hips at every follow-up appointment. We assess stem position, radiolucencies and osteolysis. The stem angle is classified as neutral, varus or valgus. A stem angle is considered neutral if its axis is within 2 degrees of the femoral shaft

axis. Femoral and acetabular radiolucencies are classified according to Gruen (Gruen et al., 1979) and DeLee and Charnley (DeLee and Charnley, 1976) zones respectively. Loosening is diagnosed if the radiolucent zone around one or both components is 2mm or more in width and a patient has symptoms on weightbearing and motion that are relieved by rest (Harkess and Crockarell, 2008). Osteolytic lesions are documented and classified on the basis of their size (linear or expansile) and their location according to previously published criteria by Zicat (Zicat et al., 1995). Of note though is that substantial interobserver variability can be expected using these systems (McCaskie et al., 1996, Kneif et al., 2005). Eradication of infection is defined as absence of clinical, serologic, and radiographic signs of infection and absence of death secondary to infection or treatment during the follow-up period. We define failure as any major operation performed in any subgroup of patients for eradication of infection, including a two-stage revision, excision arthroplasty, arthrodesis, and amputation, or the need for long-term antibiotic suppression. However, in acute cemented THA infections, we perform up to a maximum of three debridements before proceeding to any further surgical intervention or considering long-term antibiotic suppression, taking into consideration patients' comorbidities and risks for surgery and their preference for choice of treatment. We consider reinfection to be an infection with the same or another organism.

5.3 Patients and Methods

We performed a retrospective cohort analysis of a prospectively compiled register of all 204 patients diagnosed with infected THAs (127 primaries, 77 revisions) and treated according to our protocol between 1999 and 2009. Patients included 88 men and 116 women with a mean age of 66.5 years (range, 39–87 years). No bilateral infections were included in our study. The majority of patients had osteoarthritis as the underlying pathology for their primary THA. (Table 5.1)

Table 5.1 Indications for the initial total hip arthroplasty

Indication	**Number**
OA	165
Inflammatory arthropathy	12
AVN	10
DDH/SUFE/Perthes	17

OA = osteoarthritis; AVN = avascular necrosis; DDH= developmental dysplasia of the hip; SUFE: slipped upper femoral epiphysis

In revision THA patients, the original indications for reoperation after their primary procedures were aseptic loosening and wear. No patient had a previous history of infection of the affected hip, and none had prosthetic loosening or mal-alignment at the time of presentation. Comorbidities were assessed according to the ASA grading system (Little, 1995); 32 patients were Grade 1, 90 Grade 2, 80 Grade 3 and 2 Grade 4. No patients were lost to follow-up. No patients were recalled specifically for this study; all data were obtained from medical records and radiographs. Professor Haddad performed all the procedures. Minimum follow-up was 3 years (mean, 6.8 years; range, 3–12 years).

Patients in the acute group where a cemented THA was originally implanted (26 patients) underwent aggressive débridement with exchange of all mobile parts. In acutely infected cementless THAs (19 patients), we proceeded to a single-stage cementless revision arthroplasty. For both groups, the mean time between onset of hip symptoms and débridement/single stage revision was 19 days (range, 1-41 days). In acute hematogenous infections, a source of infection was identified in all patients (one upper respiratory tract infection, one lower respiratory tract infection, six urinary tract infections) and the bacteria isolated in each case was the same bacteria as cultured from the prosthetic joint.

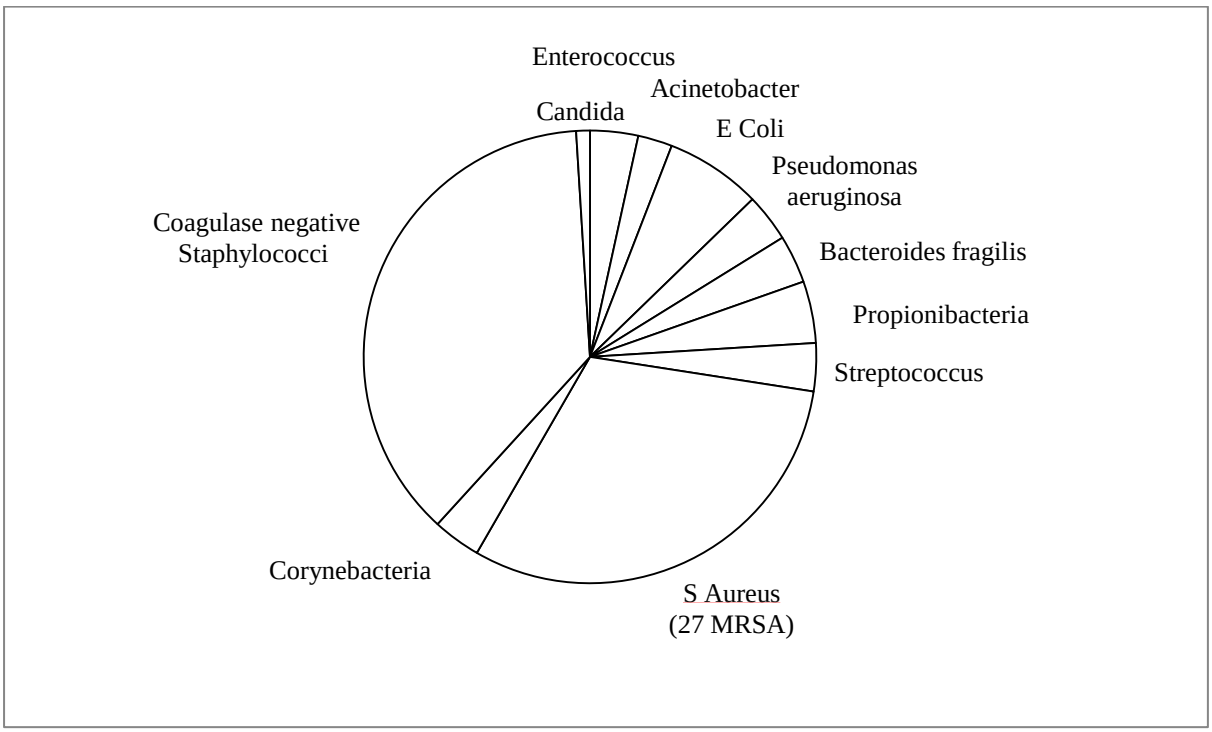
In chronic infections, we performed a single stage revision according to our preset criteria (34/159 patients) and a two-stage procedure for the rest (125 patients). In the two stage revision group, 21 patients had undergone 2 previous revisions, with 40 having one prior to 2-stage intervention. There were no prior revision procedures in the remaining 64 patients. The causative microorganism was identified pre-operatively in 104 cases whereas the remaining 21 were identified post-operatively only despite the presence of a discharging sinus in 10 cases. The mean interval time between each stage was 9 (3-36) weeks.

5.4 Results

At last follow-up, 188 of the 204 patients (92%) achieved eradication of their infections with no evidence of recurrence or loosening, wearing away, or malpositioning on follow-up radiographs.

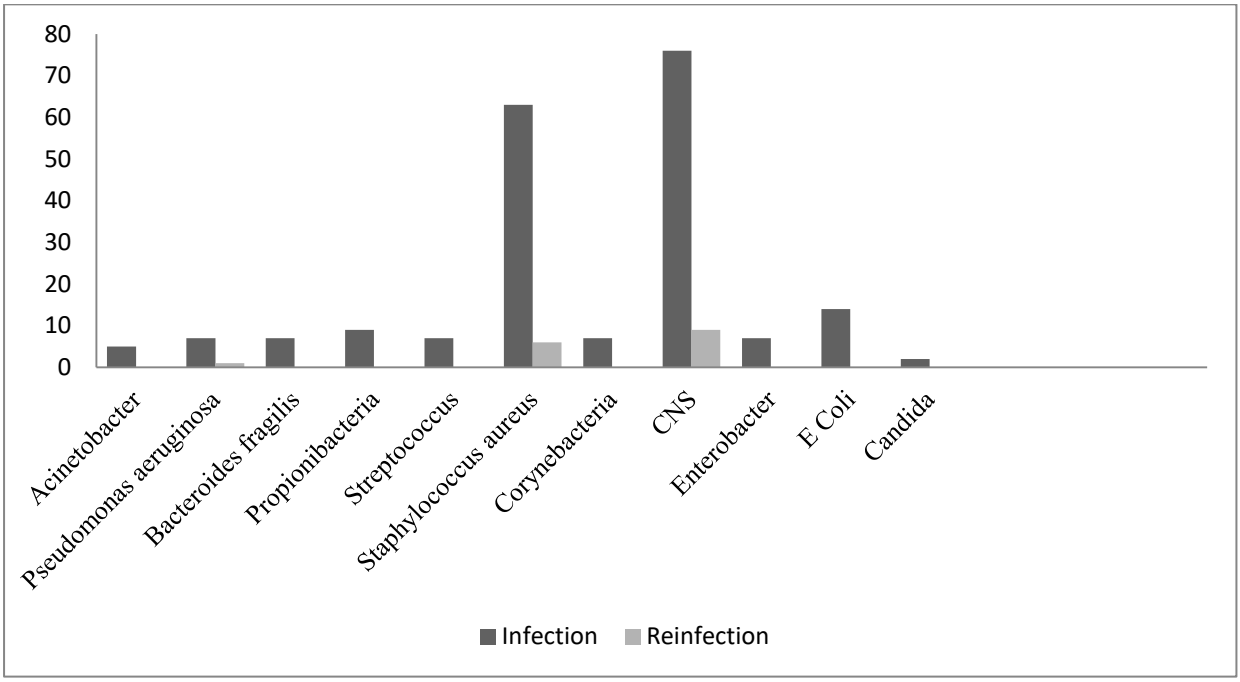
Microbiology confirmed bacterial infection in all patients, with the most commonly isolated organism being coagulase negative *Staphylococcus* (76 patients, 37%), followed by *S aureus* (63 patients, 31%), of which 27 were methicillin resistant (Figure 5.1). Other microorganisms isolated included *Streptococcus 7, Enterococcus7, Corynebacterium* spp 7, *Propionibacterium* spp 9, *Acinetobacter 5, Pseudomonas aeruginosa 7, E coli 14, Bacteroides fragilis 7 and Candida* spp 2.

Figure 5.1 Micro-organisms grown from intraoperative tissue biopsies



Most common reinfections were due to coagulase-negative *Staphylococcus* and *S aureus* (Figure 5.2).

Figure 5.2 Micro-organisms responsible for infections and re-infections



In the acute cemented THAs, eight patients had repeat washouts and the infection was eradicated in four out of the eight cases. However, five patients eventually underwent a two-stage revision due to reinfection and one patient was placed on long-term antibiotic suppression with overall 77% eradication of infection in this group of patients (we have recently published detailed analysis of those patients (Sukeik et al., 2012)]. In the acute cementless THAs, four patients underwent a two-stage revision due to reinfection with 79% infection-free survival. In the chronic THAs, no patient developed recurrence of infection in the single stage revision patients. However, six patients in the two-stage revisions developed reinfection with overall 95% eradication of infection. Of note is that all patients who had failure of their treatments underwent a further two stage revision procedure and remained

infection free at last follow up with the exception of the patient who went on long term antibiotic suppression treatment.

During the same period of follow-up, it is worth noting that there has been another 30 “haematomas” post THA which were washed out acutely with no microorganism grown from intraoperative samples and that there has been 20 “no organism” two stages that we have looked at separately with equivalent 95% eradication of infection.

5.5 Discussion

Despite the relatively low rates of PJIs after THAs, they remain a leading cause of revision surgery due to an ever increasing number of hip arthroplasties performed yearly for an aging population. (Sukeik and Haddad, 2009c) Difficulties with reaching a consensus on what defines infection and which strategy best eradicates it led to extensive variability in infection rates in the literature. Therefore, specialist tertiary centres dealing with such infections on a regular basis using a multidisciplinary approach and clearly defined protocols may improve infection-free survival and contribute to a global approach for managing PJI. We aimed at determining (1) the rates at which our protocol eradicated THA infections, (2) the most common microorganisms responsible for both infections and reinfections, and (3) the final treatment modality resulting in successful treatment of infection for each patient at the last follow-up.

Our study is associated with some limitations. First, eradication of infection after hip arthroplasties can be affected by a number of risk factors, such as age, sex, time from operation, duration of symptoms, patient comorbidities, and the pathogen causing the infection (Della Valle et al., 2004, Sukeik and Haddad, 2009c, Tsukayama et al., 1996). Because of the small number of patients within each subgroup and retrospective nature of this study, we were unable to perform a multivariate analysis to further investigate the effect of those risk factors on eradication of infection. Second, the study population was heterogeneous in relation to the type of original operation (primary versus revision), type of infection (acute versus chronic and postoperative versus hematogenous), type of prosthetic fixation (cemented versus cementless) and type of surgery performed (aggressive debridement versus single and two stage revisions).

Our results for eradication of infection using aggressive early debridement and exchange of

mobile parts for acute infections and two-stage revision for chronic infections are consistent with those previously reported in the literature especially where a clear protocol has been followed. (Brandt et al., 1997, Crockarell et al., 1998, Tattevin et al., 1999, Meehan et al., 2003, Marculescu et al., 2006, Aboltins et al., 2007, Berdal et al., 2005, Zimmerli et al., 1998, Hofmann et al., 2005, Hsieh et al., 2004, Meek et al., 2003, Younger et al., 1997, Toulson et al., 2009) It is of note, though, that the inclusion and exclusion criteria, as well as management protocols, varied among those studies, occasionally including all four types of periprosthetic infections rather than acute or chronic infections only. Additionally, some of the studies did not differentiate between hips and knees when reporting their results which resulted in a wide range of infection rates. (Table 5.2)

Table 5.2 Previous studies reporting prosthesis retention following irrigation and debridement treatment

Author	Infection Site	Number of cases	Exchange of mobile parts	Retention rate	Follow-up in years
(Azzam et al., 2010)	Hip/Knee	104	29%	44%	5.7
(Aboltins et al., 2007)	Hip/Knee	20	Partly	90%	2.7
(Aboltins et al., 2011)	Hip/Knee	17	Yes	88.2%	2.3
(Berdal et al., 2005)	Hip/Knee	18	Yes	94.5%	1.8
(Cobo et al., 2011)	Hip/Knee	103	Yes	54.3%	2.4
(Crockarell et al., 1998)	Hip	42	No	26%	6.3
(Estes et al., 2010)	Hip/Knee	20	Yes	90%	3.5
(Klouche et al., 2011)	Hip	12	Partly	75%	3.3
(Krasin et al., 2001)	Hip	7	No	71%	2.5
(Marculescu et al., 2006)	Hip/Knee	99	48%	60%	2
(Martinez-Pastor et al., 2009)	Hip/Knee	47	Yes	74.5%	1.2
(Meehan et al., 2003)	Hip/Knee	19	26%	89.5%	3.9
(Tattevin et al., 1999)	Hip/Knee	34	No	38.2%	1.6
(Tintle et al., 2009)	Hip/Knee	8	Yes	100%	3.1

(Tsukayama et al., 1996)	Hip	41	Yes	68%	6.8
(Van Kleunen et al., 2010)	Hip/Knee	18	72%	72.2%	2.6
(Zimmerli et al., 1998)	Hip/Knee	8	No	100%	2.9
The current study	Hip	26	Yes	75%	6.6

On the other hand, single stage revisions for chronic infections are regaining momentum and our results certainly reflect a strict protocol which has led to high rates of eradicating infection. (Callaghan et al., 1999, Joulie et al., 2011, Moyad et al., 2008, Raut et al., 1995, Winkler et al., 2008, Rudelli et al., 2008) Our single stage direct exchange protocol for acutely infected cementless THAs is a novel approach which has not yet gained popularity, but presents a time-limited opportunity to remove the implants prior to ingrowth in a cementless THA (Hansen et al., 2013). In comparison with aggressive debridement with exchange of mobile parts in cemented THAs, it showed superior results for eradication of infection (79% vs. 77%) with a single operation whereas a few of the cases in the debridement group required several wash outs with the additional soft tissue trauma caused before eradication of infection.

We agree that only through the use of standardised terminology that an international language of comparative results will be feasible and therefore, we support efforts made to standardise the definition of PJI (Oussedik et al., 2012, Zimmerli and Ochsner, 2003, Giulieri et al., 2004, Workgroup, 2011). However, in view of the heterogeneity of clinical presentation and variability of diagnostic tests' validity and reliability in diagnosing infection, the debate for a common strategy of treatment is yet to be finalised.

5.6 Conclusion

In conclusion, our data support the important role of specialist centres and present a clear protocol for treating periprosthetic hip arthroplasty infections against which other modalities can be tested.

Chapter 6

Discussion

6.1 Summary of Findings and Future Challenges

Despite the advances in prevention, diagnosis and treatment of PJIs, overall management remains challenging for the surgeon, patient and healthcare systems. In this thesis, having conducted a thorough literature review confirmed that prevention is the best strategy for managing PJIs. On the other hand, reaching a consensus recently to what constitutes a PJI has marked an important achievement in creating a platform for surgeons to communicate and work simultaneously in managing infections. Preventative strategies including the use of triclosan coated sutures and tranexamic acid have been explored in an RCT and meta-analysis of level one studies respectively. The most up to date diagnostic tools for PJIs have been discussed in the literature review. The role of single versus two stage revisions for chronic PJIs as well as the impact of undergoing treatment at a centre of excellence on infection-free survival has also been investigated in this thesis. A summary of our findings and future considerations are detailed in the following sections.

6.1.1 Prevention of PJIs

In order to prevent microbial colonisation of suture material in operative wounds, the triclosan coated VPS was introduced in 2002 and this has led to a reduction in both bacterial adherence to sutures and microbial viability in vitro and in animal models. Similarly, VPS had positive effects on wound healing and infection rates in a number of meta-analyses and RCTs conducted in specialties such as general and vascular surgery. However, negative effects such as dermatitis, skin irritation, allergic reactions and haematomas have also been described. Taking into consideration that no trials to date have investigated the benefits of using VPS for wound closures in orthopaedic surgery, we hypothesised that VPS may result in better wound healing characteristics and fewer infections than standard vicryl sutures in total hip and knee arthroplasty wound closures. To investigate this, we conducted a single-

centred, double-blind RCT to compare the healing characteristics of wounds closed using VPS and standard vicryl sutures in patients undergoing primary total hip or total knee arthroplasty. The primary outcome was the ASEPSIS wound scoring system and secondary outcomes included time for wound closure, length of operation, length of hospital stay, pain assessment and associated complications. Despite the premature termination of this study due to the unavailability of the sutures after December 2014, the study findings were significant to reject our hypothesis as the sensitivity analysis using the Mann Whitney test (P=0.036) as well as assessment of the wound complications at the last follow up showed significantly higher wound complication rates in the VPS group (P=0.03). We concluded that in hip and knee replacement surgery where rates of SSI are low in comparison to abdominal surgery, negative effects such as dermatitis, skin irritation, allergic reactions and haematomas may become more important and hence the advice against using the VPS in such surgeries. However, there certainly is a need for larger studies to substantiate our findings in hip and knee arthroplasty surgery and other subspecialties of orthopaedic surgery. Another area of interest requiring further research is the combination of triclosan and antibiofilms as coatings for implants to inhibit bacterial adhesion and biofilm formation. An example of biologically active antibiofilms includes deoxyribo-nuclease (DNase) I and Dispersin B which act by interrupting the physical integrity and increasing the permeability of the biofilm matrix (Kaplan, 2009, Darouiche et al., 2009). An in-vitro study of the efficacy of triclosan and Dispersin B coated vascular catheters showed synergistic antimicrobial and antibiofilm activity against *Staphylococcus aureus, Staphylococcus epidermidis* and *Escherichia coli,* significantly reducing bacterial colonisation ($P < 0.05$) (Darouiche et al., 2009). Antibiotics and metal ions such as silver have also been utilised as surface coatings to prevent biofilm formation and are worth further investigations for efficacy and durability (Park et al., 2009).

TXA has gained popularity in reducing perioperative blood loss and transfusion requirements in THA surgery. On the other hand, numerous studies have shown that allogeneic blood transfusion increases the risk of SSI and respiratory tract infections. However, no studies to date have investigated the direct relationship between TXA and wound complications including SSIs. Therefore, we conducted a meta-analysis to investigate the hypothesis that using TXA may result in less wound complications including SSIs after primary THA. The methods for this study were based on the Cochrane methodology for conducting systematic reviews and meta-analyses. The primary outcome measure was wound complications including infections. The secondary outcome measures were blood loss, the proportion of patients who had allogeneic blood transfusion, the amount of blood units transfused per patient, functional hip outcome measures, general quality of life outcome measures and complications such as DVTs, PEs, any thrombosis, renal failure, reoperation due to bleeding, non-fatal myocardial infarction, stroke and death. A comprehensive list of online databases was searched for RCTs published in any language from 1966 to April 2016. The search resulted in 21 RCTs which were appraised then data were extracted and analysed accordingly. The most significant result of this meta-analysis is the consistency of TXA in reducing wound complications after primary THAs with no heterogeneity in the studies included. The effect of TXA on wound healing has never been analysed in a meta-analysis of level one studies previously which could be an important addition to the advantages of using TXA in hip replacement surgery. Similarly, TXA reduced blood loss and allogeneic blood transfusion requirements. However, there has been significant heterogeneity among the studies evaluating these outcomes which necessitates careful interpretation of TXA effect in this context. Additionally, future randomised trials of sufficient power should be designed to examine the efficacy and safety of TXA in revision hip surgery and its efficacy in comparison to other blood conservation methods.

The growing incidence of resistant microorganisms has also led to the introduction of new antibiotics with good antimicrobial and pharmacokinetic properties. Antimicrobial therapy and eradication of infection also improved with the introduction of antibiotic loaded cement. However, using polymethylmethacrylate as the standard material for delivering depot antibiotics has raised concerns as it is surface friendly to biofilm-forming bacteria. Therefore, many biodegradable materials have been evaluated as alternatives including protein-based materials (collagen, fibrin, thrombin, clotted blood), bone-graft, bone-graft substitutes and extenders (hydroxyapatite, beta-tricalcium phosphate, calcium sulphate, bioglass), and synthetic polymers (Sukeik and Haddad, 2009a). Unfortunately, considering the limited clinical data that is currently available, the use of these materials is still experimental and clinical application should be cautious.

6.1.2 Diagnosis of PJIs

While the clinical diagnosis of PJI is not always straightforward, the lack of a gold standard test makes its diagnosis challenging. Our literature review demonstrated that the combination of various diagnostic tests into the MSIS algorithm has improved consensus and approach to managing PJIs. However, molecular biology continues to develop, and may well have an essential role in the future in identifying infection with the advantage of reducing the amount of time necessary to obtain results and commencing treatment. Synovial biomarkers under investigation for future application include cytokines such as IL-1β, IL-6, IL-8, IL-17, TNF-α, interferon-δ, and vascular endothelial growth factor, human β-defensin-2 (HBD-2) and HBD-3, and cathelicidin LL-37 (Chen et al., 2014). It is important to note that the main disadvantage of synovial biomarkers is that these tests depend on the availability of synovial fluid, and synovial fluid cannot be aspirated from a joint in all PJI cases. Moreover, some of the inflammatory biomarkers may represent any type of inflammatory process in the

prosthetic joint such as an adverse reaction to foreign material. Therefore, these tests may not be specific enough for PJI. New technologies based on biofilm targeting and the applications of metabolomics are currently underway. This includes biofilm visualisation and sequencing-based biomolecular methods, PCR-based electron spray ionization time-of-flight mass spectrometry (ESI-TOF-MS), matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bizzini et al., 2010, Jacovides et al., 2012) and BioFire Diagnostic's FilmArray system (Altun et al., 2013). Earlier PCR-based assays led to a higher rate of false-positives due to contamination and higher false-negatives because the probes could not cover the wide spectrum of pathogens responsible for infection. The use of PCR-based ESI-TOF-MS improves the utility of PCR in diagnosing PJI. For example, Jacovides (Jacovides et al., 2012) reported that using such systems not only verified positive conventional culture results, but also detected an organism in four out of five cases of PJI that was thought to be culture-negative. Additionally, 88% of the revision cases that were presumed aseptic were found to be cases that had a subclinical infection. MALDI-TOF/MS identifies bacteria via analysis of their macromolecular profile. Laser ionisation is used to measure the charge and molecular mass of the bacterial surface proteins. Since individual bacterial species have a unique mass-to-charge ratio, the obtained information is cross-matched with a bacterial spectra database (such as MALDI Bio-typer database) to identify the causative pathogen for PJI (Bizzini et al., 2010). This method is rapid and cost-effective, and has been performed on different bodily fluids (including periprosthetic joint fluid) with high agreement compared with standard methods for bacterial identification (El-Bouri et al., 2012). Another alternative to those methods is the next generation sequencing technology which enables billions of DNA strands to be sequenced in parallel, minimising the need for fragment cloning (Chiu, 2013). Unlike methods based on PCR, it does not rely on set

parameters or a panel of targets. Results are produced in 10 hours to 2 days but this technology is yet to be tested in diagnosing PJIs.

6.1.3 Treatment of PJIs

Two-stage revision remains the standard for treatment of chronic TKA infections because many series report the successful eradication of a PJI in more than 90% of patients using this approach. On the other hand, single-stage revision in selected cases has become an appealing alternative because it involves only one surgical procedure and, if comparably effective, is associated with less patient morbidity and potentially improved functional outcomes and less expense. At our institution, we carry out single-stage TKA revisions for chronic infections in very selected circumstances and therefore, our hypothesis was that a single-stage approach would be as effective as a two-stage approach if implemented in the correct patient population. We performed a retrospective cohort analysis of a prospectively compiled register of all 102 patients diagnosed with chronic infected TKAs of whom 28 (27%) were treated using a single-stage approach and 74 (73%) were treated using a two-stage approach between 2004 and 2009. Results showed that none of the patients in the single-stage revision group developed recurrence of infection, and five patients (7%) in the two-stage revision group developed reinfection ($p = 0.16$). Those patients, however, underwent a further two-stage revision procedure and had their infections eradicated at last follow-up. The Knee Society score was also higher in the single-stage group at 2 years than in the two-stage group (mean 88 (range 38-97) versus 76 (range 29-93, $p < 0.001$). We concluded that the use of single-stage revision surgery in chronic TKA infections provides high rates of infection-free survival when patients are carefully selected. However, larger, multicenter, prospective trials are called for to validate our findings.

Specialist tertiary centres dealing with PJIs on a regular basis using a multidisciplinary approach and clearly defined protocols may improve infection eradication rates and contribute to standardising management of PJI after THA. Our hypothesis was that treatment of infections at a centre of excellence improves overall infection rates. We investigated this by performing a retrospective cohort analysis of a prospectively compiled register of all 204 patients diagnosed with infected THAs (127 primaries, 77 revisions) and treated according to our protocol between 1999 and 2009. In acutely infected cemented THAs where the components are well fixed, we perform an aggressive open débridement with exchange of mobile parts and retention of the implant. In acutely infected cementless THAs, when the infection is secondary to haematogenous spread in previously well functioning and well fixed implants, we follow the same protocol for cemented prostheses. However, in acute postoperative infections, once the debridement is complete we then proceed to a direct exchange single-stage cementless THA. In chronic PJIs, the standard treatment is a two-staged revision procedure. However, in a highly selected subset of patients, a single-stage approach is utilised and has proven to provide high rates of eradicating infections. At last follow-up, 188 of the 204 patients (92%) achieved eradication of their infections and returned to their expected functional level with no evidence of recurrence or loosening, wearing away, or malpositioning on follow-up radiographs. Our results compare well with various treatment strategies reported in the literature. We therefore concluded that management of PJI at tertiary centres with the appropriate setup of a multi-disciplinary team dealing with infection on a regular basis improves infection-free survival and patient outcomes. The next step would be to collaborate at an international level between these centres to establish a common pathway for managing PJIs taking into consideration local differences in microbiology but eliminating patient, surgeon and healthcare system factors which often prevent reaching a consensus.

Alongside the above recommendations for treatment of PJIs, a number of adjuvant therapies are currently being tested and may have an essential role in the future in improving treatment of PJIs. These include bacteriophage (Kaur et al., 2014) and photodynamic therapy (Saino et al., 2010), the use of magnetic (Ercan et al., 2011) or electric currents (Ueshima et al., 2002), shockwave treatment (Hansen et al., 2012) and bioactive glass (Drago et al., 2013).

6.1.4 Conclusion

In summary, there are continued efforts to advance diagnostics and therapeutic strategies in treating PJIs but this remains much more expensive then prevention as a management strategy. Using triclosan coated sutures does not have a protective effect against infection. On the contrary, it has been associated with higher rates of wound complications and infections. TXA has led to a reduction in the risk of developing wound complications including infections compared to the control group. The use of treatment strategies such as the single stage approach in selected patients and treating PJIs at specialist centres also contribute to successful treatment of PJIs.

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Appendices

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Appendix 2.1 Patient Information Sheet

A randomised controlled trial of triclosan coated sutures in primary total hip and total knee arthroplasty

Dear Sir or Madamme,

You are being invited to take part in a research study. Before you decide if you want to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. It is totally voluntary and up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Thank you for reading this.

1. What is the purpose of the study?

Although safer than ever, infections after hip and knee replacements remain a challenging problem. Managing such infections often requires a long course of treatment and can lead to unhappy patients with poor function of the joint. We are always looking for ways to prevent infection, as it has been proven that prevention, rather than treatment, provides the best outcome for our patients.

The purpose of this study is to find out whether sutures (stitches) coated with an antiseptic agent called triclosan are able to reduce infections within a surgical wound, in people having total hip and total knee replacements. Triclosan is not a new drug and has been used for more than 30 years in toothpaste, cosmetics and antiseptic soaps. Triclosan-coated sutures have been successfully used to reduce infections after heart surgery, abdominal surgery and neurosurgery. We hope that the use of triclosan-coated sutures will work in a similar way when used in total hip and total knee replacements.

To be able to determine the effect of triclosan-coated sutures in total hip and total knee replacements, we need to compare the number of infections between those who are given the new suture and those who are given regular sutures.

If you agree to enter this study, you will be placed in one of the two groups. One group of participants will receive triclosan-coated sutures during surgery and a second group will receive an ordinary suture without triclosan. The group you will go into will be chosen at random (like a spin of a coin). Neither you nor the investigator will know which group you are in. At the end of your operation the deep layers of the wound (which you will not be able to see) will be stitched using either the triclosan-coated suture or the ordinary suture. The outside skin (which you will be able to see) will be closed as normal, using clips for both groups. This is the only difference between the two groups. You will then receive our standard postoperative treatment, for people undergoing total hip or total knee replacements.

2. **Why have I been chosen?**

Your surgeon has decided that you need a total hip or total knee replacement. We would like to invite you to take part in this study. We would like to recruit 420 patients, over a period of 24 months.

3. **What do I have to do?**

Your participation is voluntary but there will be an extra clinic for you to attend at the hospital 2 weeks after the operation for inspection of the wound and removal of the skin clips rather than having that done at your GP surgery. Additionally, at the time of discharge you will be given a simple ‘yes/no’ questionnaire regarding your wound, which you will be asked to complete and return in a pre-paid envelope two months after the operation. If you do decide to participate, you may withdraw at any time and you do not need to give a reason. Whatever you choose to do will not affect your treatment in anyway.

4. **What are the side effects of triclosan?**

Minimal inflammation of the surrounding tissues, localised irritation when skin sutures are left in place for greater than 7 days (sutures used in this study will only be used to close the deep layers of the wound as detailed above), and slower absorption (>70 days) in tissues with poor blood supply as well as allergic reactions in the form of a rash or contact dermatitis have been reported with the use of triclosan. One study showed that triclosan-coated sutures increased the risk of wound separation in breast surgery. However, this was not supported by findings from other studies. Whilst rarely serious, the occurrence of any side effects will be sought while you are in hospital and at each subsequent hospital visit. You will be asked about hospitalisations, consultations with other medical practitioners and appropriate treatment will be provided according to the underlying problem.

5. **What are the possible benefits of taking part?**

We do not know for certain if triclosan-coated sutures will improve the wound healing or reduce infection rates in total hip and total knee replacements. However, there is a chance that these sutures will improve recovery time and joint function for hip and knee replacements. There may not be any benefit to you directly if you are placed in the group which will receive an ordinary suture without triclosan.

6. **What if something goes wrong?**

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, the National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, compensation may be available.

If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Professor Fares Haddad who is the Chief Investigator for the research and is based at University College Hospital. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

7. **Will my taking part in this study be kept confidential?**

If you consent to take part in the research any of your medical records may be seen by our research team for purposes of analysing the results. They may also be looked at by people from regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital. Although this study is not conducted by your GP, your GP will be told of your participation in the trial.

8. **What will happen to the results of the research study?**

At the end of the study, we will look at the results and compare the two groups of patients to see whether the triclosan-coated suture has any benefits. If it has, we will try to implement this in our clinical practice. We may publish the study in the medical journals to benefit other people. If we do so, you will not be identified in any report or publication.

9. **Who is organising and funding the research?**

This study is organised and funded by the Trauma and Orthopaedic Directorate at University College London Hospitals, and has not received any external funding. Your doctor will not be paid for including you in this study.

10. **Contacts for Further Information**

For any further information, please contact one of the following:

Mr M Sukeik, Mr D George, Mr A Gabr, Mr R Kallala, Dr APR Wilson, Professor FS Haddad

Department of Trauma and Orthopaedics

University College London Hospital

Ground Floor Central, 250 Euston Road

London, NW1 2PG, Tel 020 7380 9413 Fax 020 7908 2060

Thank you for considering taking part in this study.

University College London Hospitals NHS
NHS Foundation Trust

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Appendix 2.2 Consent Form

CONFIDENTIAL

Patient Identification Number for this study:

UCL Project ID number:
Form version: 8.0

Version Date: 07/05/2013

Title of project: **A randomised controlled trial of triclosan coated sutures in primary total hip and total knee arthroplasty**

Name of Principal investigator: Professor FS Haddad

1. I confirm that I have read and understood the information sheet dated 07/05/2013 (version 8.0) for the above study and have had the opportunity to ask questions. ☐

2. I confirm that I have had sufficient time to consider whether or not want to be included in the study ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

5. I agree that my GP is informed of my participation in the study. ☐

6. I agree to take part in the above study. ☐

Name of Principal investigator: Professor FS Haddad

_____ _____ _____

Name of patient Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

(if different from researcher)

_____

Name of the researcher to be contacted if there are any problems

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCL project number at the top this consent form.

1 form for Patient;

1 to be kept as part of the study documentation,

1 to be kept with hospital notes

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NHS Foundation Trust

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APPENDIX 2.3 GP Questionnaire

Dr Date:
GP Surgery

Dear Dr,

Re: Patient name Hospital No: Date of birth:

University College London Hospital is running a randomised controlled trial to compare the healing characteristics of polyglactin 910 triclosan (antibacterial) coated sutures (treatment of interest) and polyglactin 910 sutures (routine care) in patients aged 18 or over undergoing primary unilateral hip and knee arthroplasty.

Your patient, *patient name*, agreed to take part in the trial and was randomised to receive *treatment of interest / routine* care when they attended hospital on *date of attendance*. Apart from the use (or not) of the treatment of interest they will receive the standard treatment for *hip/knee* replacements by hospital doctors.

They will also attend our arthroplasty clinic at 2 weeks postoperatively for inspection of the wound and removal of the clips. Additionally, they will be sent a postal questionnaire survey at two months after hospitalisation, and then their involvement in the trial will end. The questionnaire will consist of an assessment of the patient's wound healing.

If you would like any further information about this project, please contact me using the details above.

Yours sincerely

Mr Mohamed Sukeik

APPENDIX 2.4 Data Collection Sheet

Randomisation code:	**Patient label**

Patient characteristics and risk factors affecting wound healing

Diagnosis	**Gender**	**Age**	**BMI**	**Smoking**	**Diabetes**	**ASA**	**Length of operation (min)**

Surgical data and secondary outcomes measured

Operation	THR / TKR	**Time for wound closure (min)**	
Surgeon level	Consultant SpR Fellow Staff Grade	**Length of hospital stay (days)**	
Type of anaesthesia **(including local anaesthetic infiltration)**	General /Regional Local anaesthesia Yes / No	**Visual Analogue Score (1-10)**	Day 1 Day 3 Day 5
Type of antibiotic prophylaxis and dose regimen		**LMWH prophylaxis**	Yes / No
Type of prosthesis		**Number of sutures used**	

Postoperative complications

Complication	**Tick if present**	**Complication**	**Tick if present**
Nausea and vomiting		**Chest infection**	
Dizziness		**Myocardial infarction**	
Bleeding		**Cerebrovascular accident**	
Stiffness		**Fracture**	
Neurovascular damage		**Dislocation**	
Deep venous thrombosis		**Loosening of prosthesis**	
Pulmonary embolism		**Mortality**	
Other complications/ Serious adverse events			

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APPENDIX 2.5 Post-discharge Questionnaire

Dear Patient,

Re: **Follow up on the progress of your wound:**

Hospital Number: **Date of operation:**

We saw you in hospital some time ago to see how your wound site was getting on. As some wounds cause a few problems once a patient goes home, we'd be grateful if you would fill out this questionnaire if your operation was at least 1 month ago. The information you give us will help us to plan and improve our patient care.

Have the wounds healed without any problems at all? Yes No

If "yes" please ignore the following questions. If "no" please answer the following:

- Has the wound been red? Yes No
- Has the wound discharged clear yellow fluid? Yes No
- Has the wound discharged pus? Yes No
- Has the wound broken open? Yes No
- Have you been given antibiotics for wound infection? Yes No
- Has a district nurse had to dress the wound? Yes No
- Has a doctor opened/drained an abscess? Yes No
- Have you been admitted to hospital elsewhere? Yes No
- Has the wound been opened and cleaned under general anaesthetic in hospital? Yes No

Thank you for your help

Yours sincerely,

A.P.R. Wilson, MA, MD, FRCPath, FRCP
Consultant Microbiologist

University College London Hospitals NHS
NHS Foundation Trust

Department of Orthopaedics
University College Hospital
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APPENDIX 2.6 MHRA Letter

Subject: RE: Scope - protocol review - coated polyglactin 910 sutures with triclosan - Our ref: E/2010/0691
Date: Tue, 20 Jul 2010 14:37:49 +0100
From: Daniella.Smolenska@mhra.gsi.gov.uk
To: msukeik@hotmail.com

Dear Mr Sukeik

Thank you for your email below. I can confirm that a product which is primary intended to act as a suture will most likely be regulated as a medical device.

From our telephone conversation last week I understand that the coated sutures subject to the investigation are CE marked. As such I can confirm that as long as the devices are CE marked for the purpose under investigation there will be no requirement to obtain MHRA authorisation for this study.

Please note that whilst we are willing to give any help and advice we can, any views given by us on the interpretation of the Medical Device Regulations represent our best judgement at the time, based on the information available. Such views are not meant to be a definitive statement of law, which may only be given by the Courts. Accordingly we would always advise you to seek the views of your own professional advisors.

I hope that this has answered your questions, however if you require further guidance please contact me again.

Kind regards
Daniella

Daniella Smolenska
Regulatory Affairs Manager
Market Towers room 8/2-A07
1 Nine Elms Lane
Vauxhall
LONDON SW8 5NQ
Tel: +44 (0) 20 7084 3363
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APPENDIX 2.7 UCLH Research and Development Department Approval

University College London Hospitals NHS
NHS Foundation Trust

Joint Research Office

Office Location:
1st Floor Maple House
149 Tottenham Court Road
London W1T 7DN

Postal Address:
UCL,
Gower Street
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Tel: 020 3447 72177/79833 Fax: 020 3447 9937
Websites: www.uclh.nhs.uk; www.ucl.ac.uk; www.ucl.ac.uk/jro

FINAL R&D APPROVAL – NHS PERMISSION

07/06/2013

Mr Mohamed Sukeik
University College London Hospitals NHS Foundation Trust
235 Euston Road
London
NW1 2BU
UK

Dear Mr Sukeik,

Project ID: 11/0011 (Please quote in all correspondence)
REC Ref: 13/LO/0435
UKCRN ID:
Title: A randomised controlled trial of Polyglactin 910 Triclosan coated sutures versus standard Polyglactin 910 sutures in patients aged 18 or over undergoing primary unilateral hip and knee arthroplasties in the Department of Trauma and Orthopaedics at University College London Hospital

Thank you for registering the above study with the Joint Research Office (UCLH site). I am pleased to inform you that your study now has local R&D approval (NHS permission) to proceed and recruit participants at University College London Hospitals NHS Foundation Trust subject to sponsor confirmation.

Please note that all documents received have been reviewed and this approval is granted on the basis of the key documents provided which are ethically approved by the Research Ethics Committee:

Document	Date
REC approval and REC approved documents	03/06/13

As Principal Investigator you are required to ensure that your study is conducted in accordance with the requirements on the attached sheet. These include the conditions of your NHS permission.

Do not hesitate to contact a member of the team should you have any queries.

Yours sincerely

[redacted]

Professor Monty Mythen
Director of Research and Development
UCL/UCLH/Royal Free Joint Research Office

uclh University College Hospital | National Hospital for Neurology and Neurosurgery | Eastman Dental Hospital | Royal National Throat, Nose and Ear Hospital | Heart Hospital | Royal London Hospital for Integrated Medicine

APPENDIX 2.8 Regional Ethics Committee Approval

NHS
Health Research Authority

NRES Committee London - Harrow
Bristol Research Ethics Committee Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173 421383
Facsimile: 01173 420455

03 June 2013

Professor Fares Sami Haddad
Professor in Orthopaedics
University College London Hospital
235 Euston Road
London
NW1 2BU

Dear Professor Haddad

Study title:	**A randomised controlled trial of Polyglactin 910 Triclosan coated sutures versus standard Polyglactin 910 sutures in patients aged 18 or over undergoing primary unilateral hip and knee arthroplasties in the Department of Trauma and Orthopaedics at University College London Hospital**
REC reference:	**13/LO/0435**
IRAS project ID:	**67960**

Thank you for your letter of 07 May 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Libby Watson, nrescommittee.london-harrow@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

NHS
Health Research Authority

- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/LO/0435 **Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

[redacted]

Dr Jan Downer
Chair

Email:nrescommittee.london-harrow_nrescommittee.southcentral-hampshireb@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr David Wilson*
Miss Shahina Begum-Meah, UCLH/UCL Joint Biomedical Research Unit