Prevention of pin site infection using a novel antimicrobial-impregnated collar

Jennie A. Walker
MSc, BSc Hons, RN, PGCert Med Ed

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

October 2015

Abstract

Background and aims

Pin site infection (PSI) is a common complication of external fixation which can cause significant morbidity. Additional treatment required as a result of PSI can be costly in terms of NHS time and resources, but also personal and financial losses for those undergoing additional treatment. A reduction in PSI would therefore reduce the complications and costs associated with infection. The aim of the study is to determine the feasibility of antimicrobial impregnated collars in preventing PSI in patients with external fixation.

Methods

Current pin site care practices were identified by using an electronic questionnaire. Assessment of bacteria present at clinically non-infected and infected pin sites was determined through evaluating swabs obtained from the out-patient setting. Bacterial isolates were tested for antimicrobial sensitivity and biofilm capacity.

Pre-clinical testing of the antimicrobial collar used bacterial isolates identified from the PSI evaluation. Test strains included *S aureus*, *S epidermidis*, corynebacteria and *E coli*. Pre-clinical tests included SPTT, tK100, and an in-vitro pin site model.

A single-centre randomised control feasibility study was conducted with participants allocated to standard care or antimicrobial collar. Primary endpoints included number of participants with PSI, number of infected pin sites and bacteria present at pin sites at 3 months.

Main findings

Pin site care remains varied across the UK despite the availability of the UK Consensus Guidelines (Timms et al 2011). Pin site care is also inconsistent internationally. The bacterial evaluation identified large number of CoNS (46.2%), corynebacteria (10.7%) and *S aureus* (4.1%) in clinically non-infected pin sites, although the significant increase of *S aureus* to 17.9% in PSI ($p<0.01$) suggests that this is a key causative organism in PSI. Antimicrobial sensitivity testing identified that 91.9% CoNS were sensitive to at least two of the antimicrobials used in the collar indicating that the antimicrobial collar has the potential to prevent PSI. SPTT demonstrated the efficacy of the antimicrobial collar in maintaining a zone of bacterial inhibition in excess of three months. TK100 methods also demonstrated the ability of the antimicrobial collar to kill attached bacteria within 72 hours.

The feasibility study identified poor participant compliance with the antimicrobial collar. Participants in the antimicrobial collar group had significantly reduced bacteria at pin sites when the antimicrobial collar was retained in place for the duration of treatment ($p=0.01$). No significant difference was detected with number of participants with pin site infection or number of infected pin sites.

Conclusion

Results from preliminary testing indicates that the antimicrobial collar may be effective in reducing PSI in participants with external fixation, however further product development is required prior to rigorous testing with an adequately powered randomised control trial and economic evaluation.

Declaration

This is to certify that the work submitted in this thesis is the result of research conducted by the candidate. The following assistance was received with the work presented in the thesis:

- The concept of the antimicrobial collar and trial was conceived by Professor Roger Bayston.
- Study approval, ethical application, participant recruitment, data collection, data analysis and writing were conducted primarily by the candidate with support from supervisors Professor Bayston and Professor Scammell.
- The Nottingham clinical trials unit generated randomisation codes for participant enrolment, and received payment for their services.
- Advice of data analysis was received from Dr Andrea Venn.
- Scanning electron microscopy was conducted by Christine Grainger-Boultby

This work has not been submitted for any other degree or other professional qualification. Supervision of this thesis was undertaken by Professor Roger Bayston and Professor Brigitte Scammell.

Acknowledgements

I would like to thank Professor Roger Bayston and Professor Brigitte Scammell for the opportunity to complete this work. Thank you for your time, continual support and guidance. I would also like to thank Arthritis Research UK for the Allied Health Professional Grant which made the research possible.

Sincere thanks also to the Trauma and Orthopaedic team at Nottingham University Hospitals NHS Trust for their continued help and support with the study, without whom the study would not have been possible. I am most grateful to the staff within the Academic Division of Trauma, Orthopaedics and Sports Medicine who have cared and offered support in so many ways along the journey. A special thanks also to the BRIG members whom I have had the pleasure to work alongside throughout my studies. Thank you to Waheed Ashraf for his help with HPLC, Christine Grainger-Boultby for her help with SEM imaging and Dr Andrea Venn for her help with my many questions on statistical analysis.

I would finally like to thank my husband and children for never complaining about the amount of time I spent working and of course for all their encouragement to complete this work, for which I am eternally grateful.

Contents

Index of Figures

Index of Tables

Abbreviations

ABB	Anaerobic basal broth
cfu	Colony forming Units
CoNS	Coagulase negative Staphylococcus
CRP	C-reactive protein
HA	Hydroxyapatite
HPLC	High performance liquid chromatography
ISA	Iso-Sensitest agar
ITT	Intention to treat
L	Litre
mg	Milligram
MIC	Minimum inhibitory concentration
mL	Millilitre
Mm	Millimetre
MPC	Mutant prevention concentration
OD	Optical density
PBS	Phosphate buffered saline
PPI	Patient and public involvement
PSI	Pin site infection
SEM	Scanning Electron Microscopy
SOP	Standard operating procedure
SPTT	Serial plate transfer test
SS	Stainless steel
tK100	Time to Kill 100% bacteria
TSB	Tryptone Soya Broth
TSF	Taylor spatial frame
µg	microgram
µL	microlitre
ZoI	Zone of inhibition

Chapter 1 Introduction

1.1 External Fixation

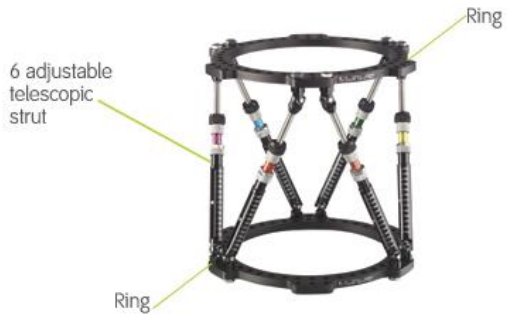
External fixation is a minimally invasive technique which involves the percutaneous insertion of pins and/or wires into or through bone. These are secured using clamps or connectors to bars or circular rings to create a stable device. External fixation can be used in various situations such as temporary fixation of severe open fractures (also referred to as 'damage control'), definitive management of complex fractures, or where there has been extensive bone loss (Edwards et al 2002). External fixation also provides an alternative method of stabilisation where internal fixation is not appropriate, for example patients with poor soft tissue integrity, localised infection or patients who are not systemically optimized for lengthy surgery (Thiryayi et al 2010). Limb lengthening, correction of complex deformities and treatment of mal-union can also be managed using external fixation (El-Mowafi 2004; Basbozkurt et al 2005).

Circular frames may refer to Ilizarov, Taylor spatial frame (TSF) or similar models (Figures 1.1 and 1.2). The circular frame design allows placement in close proximity of a joint and permits adjustments to enable correction of the fracture or deformity. The design of the TSF struts permits multi-axial correction without the need for frame reconstruction, making correction relatively simple following initial application of the frame (Marangoz et al 2008; Nakase et al 2009).

Figure 1.1 Ilizarov external fixator

http://www.mistngo.org/category/gallery/medical

Figure 1.2 Taylor spatial frame (shown without wires)



http://www.smith-nephew.com/patient/treatments/limb-restoration

Unilateral frames (Figure 1.3) use a pin and bar fixation method, although hybrid unilateral fixators may use a combination of pins and wires.

Figure 1.3 Unilateral external fixator

www.smith-nephew.com/professional/products/trauma/jet-x/jet-x-bar

Halo immobilisation can be used to stabilise cervical spine injuries, or instabilities occurring secondary to other pathology, such as neoplasm, infection or rheumatoid arthritis. Halo immobilisation involves the insertion of pins to the outer table of the skull and attachment to a rigid vest in order to create a firm construct which immobilises the cervical spine (Figure 1.4.).

Figure 1.4 Halo vest immobilisation

http://www.opentip.com/Sporting-Goods/Halo-Vest-Assembly

The point where the pin or wire exits the skin is referred to as the pin site or wire site. For the purpose of this document all pin and wire insertion points will be referred to as pin sites.

History of external fixation

Wutzer successfully first treated femoral non-union with a gold wire cerclage in 1846 (Bartonicek 2010) and external fixation was notably used by Key (1932) for knee arthrodesis in tuberculosis patients. Charnley (1951, 1958) later used external fixation with pins to increase fusion rates and decrease consolidation time following knee arthrodesis and Hoffman further popularised the use of external fixation in the 1950's stabilizing long bone fractures (Fragomen and Rozbruch 2007). During this era Ilizarov was developing his techniques using fine wire external fixation techniques to successfully treat tibial non-union (Spiegelberg et al 2010).

External fixation has traditionally been associated with problems of non-union, mal-union and infection due to poor understanding of the application and fracture healing principles (Ziran et al 2007). The complexity of treatment is amplified with the difficult patient population for which this technique was reserved – i.e. those with severe injuries, or cases complicated by infection. It is therefore not unexpected that historically complication rates were higher with external fixation than the more routine interventions utilised in less complex cases. Complications of external fixation are discussed in section 1.2

Principles of external fixation

The pin-bone interface is the point of maximum stress during loading and is considered the weakest component within the fixator (Capper et al 1994). Pin design and insertion are therefore of fundamental importance to the integrity and durability of the fixator. Pins may be chosen according to the material, shape, and profile of the thread as well as the heat generated during insertion and the torque obtained (Hedin and Larsson 2004). The choice of frame, pins and wires is often dependent on clinician preference, clinical situation and availability of resources. Where possible external fixators should have maximum versatility for managing the injury and allow maximum functionality of the patient (De Bastiani et al 1984 and Hedin and Larsson 2004).

Antoci et al (2008) evaluated the incidence of PSI during limb lengthening using external fixation and observed significantly more PSIs in half-pin fixators (100% frames) when compared to hybrid fixators with (78% frames), with the incidence of infection reported as 78% for pin sites and 33% for wire sites. In contrast to this Inan et al (2004) reported a higher number of insertion sites which required removal following pelvic support

osteotomies due to infection in Ilizarov frames, compared to monolateral external fixator frames (5 v 1). Catagni et al (2006) reported similar rates of PSI between wires (4.73%) and half-pins (3.11%). The heterogeneous nature of these studies makes evaluating differences in pin/wire infection rates complex, and therefore requires further research.

Duration of treatment

Duration of external fixation varies according to the nature of injury and contributing factors such as co-morbidities or infection. Injuries treated with so called 'damage control' orthopaedic devices may have fixators in place for several days until the soft tissues are suitable for definitive fixation or the patient is systemically optimized for more lengthy surgical intervention. External fixation of fractures may range from several weeks to many months in the case of non-union or in the presence of infection. Vasiliadis et al (2009) reported average treatment time in an Ilizarov device as 11 weeks (range 9-14 weeks) for distal tibial intra-articular fractures whereas Kocaoğlu et al (2001) reported an average time of 11.7 months (range 5-48 months) for treatment for a humeral shaft non-union.

1.2 Complications of external fixation

Complications associated with external fixation include infection, nerve injury/palsy, breakage of pins/wires, pin loosening, delayed union, mal-union, re-fracture, joint stiffness and contracture (Lerner et al 2005; Hedin and Larsson 2004). Halo immobilisation complications include pin loosening, intracranial pin penetration, infection, cranial palsy, dysphagia, and loss of reduction/position (Papagelopulos et al 2001).

Some of these risks can be minimised with careful placement of pins and wires to avoid neurovascular injury and appropriate involvement of the multidisciplinary team to prevent joint stiffness and contractures developing (Narayan and Marsh 2003).

Pin loosening

The relationship between pin loosening and PSI is unclear with varying results reported within the literature. The longer the pin is in-situ the greater potential there is for deterioration in the bone-pin fixation (Moroni et al 2002a); however, it remains unclear as to what part pin loosening plays in PSI. Various methods have been studied to reduce pin loosening such as the configuration of pins, pin material or pin coatings (Karnezis et al 1999, Moroni et al 1998, Moroni et al 2002b, Placzek et al 2006, Pizà et al 2004, Pommer et al 2002).

Van Middendorp et al's (2009) prospective study of 239 patients in halo immobilisation concluded that pin loosening was not significantly related to the development of PSI ($p=0.135$), with 12% ($n=29$) experiencing PSI and 7% ($n=17$) experiencing pin loosening. Similarly, Pizà et al (2004) reported reduction of pin loosening in limb lengthening techniques with hydroxyapatite (HA) coated pins, although no significant difference in PSI. Ganser et al (2007) also reported no significant difference between stainless steel (SS) or titanium pins regarding looseness or PSI using a sheep model.

Ahlborg's (1999) retrospective analysis of 314 distal radial fractures reported an overall complication rate of 27%, with PSI being the most common complication (21%, $n=65$). Nine cases required premature fixator removal with a reported mean fixation time of 28 days (range 15-38 days) compared to the overall mean fixation time of 39 days (range 7-122)

p=0.0007. Pin loosening was higher in women over the age of 75 years (p=0.009), with no difference in the frequency of antibiotic use, pin site fracture or removal of external fixation. As this patient group are predisposed to osteoporosis these findings may relate to poor bone quality associated with osteoporotic changes. Pieske et al (2008) have also noted increased pin loosening with advancing age and demonstrated superior properties of HA pins in preventing pin loosening in comparison to SS (p=0.018) (Pieske et al 2010).

Moroni et al (2001) investigated the clinical benefit of HA pins in reducing pin-related complications compared to SS pins. Pin loosening was less with HA pins and PSI was significantly higher with SS pins (p=0.009). In contrast to this Pieske et al (2010) observed no significant difference in pin site complications between either group (p=0.284), although observed a higher incidence of PSI with loose SS pins than with loose HA pins. While the studies compared similar pins and complications with similar size study groups, the methodology makes true comparison of the results more challenging. Patients in the Moroni study had a mean external fixator time of 147 days compared to 6 weeks in the Pieske study, which may influence the number of complications observed. Differences also exist with the classification of PSI. Moroni utilised the Checketts and Otterburn classification tool (Checketts and Otterburn 1992), whereas Pieske developed criteria which considered erythema, drainage, pain, oral antibiotics, pin site care and the need for hospitalisation. Pin site care also varied between studies. These differences therefore limit the generalisations which can be made from these findings.

Pin loosening and infection are common problems associated with external fixator devices, although the relationship between these outcomes and pin materials requires further investigation.

Psychological non-acceptance

Acceptance of the external fixator device may be challenging for some patients due to altered body image (Patterson 2010). These patients may find it difficult to engage with management strategies and adhere to recommended care regimes. Factors such as depression and destructive behaviour need to be considered carefully when planning to discharge patients from hospital to care for their own pin sites and frame between hospital visits (Patterson 2006). Richards et al (2015) noted that 9% of their paediatric patients developed anxiety or depression during limb reconstruction, which clearly highlights the need for frequent psychological assessment during treatment.

Patients may be embarrassed by the dependency induced by the frame and be reluctant to seek help (Limb 2004). Much of the nursing and medical literature focus on the care of the pin site/fixator, yet psychosocial issues are rarely considered despite being an important factor which can directly impact upon self-caring activities (Limb 2003).

1.3 Infection

Initial trauma and the insertion of pins/wires disrupt the skin's natural barrier defence against bacteria. Although insertion sites are often colonised, infection can occur when there is an imbalance between an overwhelming number of virulent bacteria and local defence mechanisms (Robson 1979). Infection of the pin site may range from local soft tissue infection and cellulitis to osteomyelitis, septic arthritis and in severe cases septicaemia (Fragomen and Rozbruch 2007). Common pathognomonic signs include fever, raised white cell count and raised C-reactive protein

(CRP) (Tiemann and Hofmann 2009). In advanced osteomyelitis a sequestrum may also be identified on radiographs.

Significantly higher infection rates have been reported with percutaneous Kirschner wires than those buried under the skin ($p=0.02$) (Hargreaves et al 2004). This highlights the potential for bacteria to contaminate the pin/wire above the pin-skin interface and track down below the surface and cause infection. In many cases minor infection can be remedied with increased pin site care and oral antibiotic therapy. Deep infection may result in osteomyelitis, bacteraemia, bacterial endocarditis and toxic shock syndrome (Antoci et al 2008), which require systemic antibiotics.

Predisposing factors

Tiemann and Hofmann (2009) propose that the occurrence of osteomyelitis may be partly due to endogenous factors such as obesity, alcohol/nicotine abuse, immunosuppressive therapy and being over 65 years of age. Exogenous factors vary although the susceptibility of soft tissues and bone to infection following trauma or surgical manipulation is of key importance. Bacteria can be introduced to the fixation site during the initial trauma in the case of open injuries, during the insertion of pins, or during the ensuing time where the external fixator remains in-situ.

Prevalence of PSI is known to correlate with the thickness of soft tissue overlying the bone (Moroni et al 2002b) and potentially greater motion at the skin-pin interface (Inan et al 2004). Thermal damage from pin insertion may lead to necrosis and consequently increase the risk of pin loosening and PSI (Hutchinson et al 2000). Haematogenous spread of bacteria is also a potential mode of contamination and risk for developing PSI (Montanaro et al 2007). Smoking is associated with a higher incidence

of complications and prolonged fixation times (W-Dahl and Toksvig-Larsen 2004) due to decreased tissue oxygenation and delayed bone healing.

Advancing age may signify an increased risk of infection due to the presence of multiple co-morbidities, such as chronic renal failure, peripheral vascular disease and ulcers, which can predispose to infection. The ability to self-care and manage pin sites independently may also be a contributory factor in developing infection, which as yet has not been directly addressed in the literature. Interestingly, in contrast, Rogers et al (2007) found that patients of an older age were less likely to experience complications associated with their external fixator. The average age of those with complications was 51 compared to 64 years in those without complications. The authors suggested that this may be attributable to the increased rehabilitation and activity of younger patients, which may lead to an increased risk of infection, wound dehiscence and pin fracture. Patients with a raised pre-operative glucose levels were also more likely to develop PSI or wound dehiscence ($p=0.02$).

Classification of pin site infection

Classification of PSI varies within the literature, with some studies using clinical judgement of infection (Katsenis et al 2005) and others preferring to use microbiological diagnosis of infection (Pommer et al 2002). There are various problems associated with the clinical diagnosis of PSI, such as inter-observer reliability and lack of validated criterion to diagnose infection. This is particularly pertinent when differentiating between inflammation and irritation due to the presence of a pin/wire and the inflammatory response in the presence of infection (Santy 2010). The use of a clinical assessment tool or grading criteria can improve the reliability and reproducibility of assessment by reducing the variability in how pin sites are assessed for signs of infection. The use of clinical assessment

tools can also provide objective assessment of the pin site which can be monitored over the course of treatment to not only identify the presence of infection, but monitor the response to treatment.

A Cochrane review on pin site care for preventing infection has highlighted the lack of validated assessment tools for identifying PSI (Lethaby et al 2013). The use of diverse research methodologies and classification criteria subsequently makes critical evaluation of intervention and cause-effect relationships difficult to interpret and apply into clinical practice.

Lee-Smith et al (2001) attempted to differentiate between a skin reaction, colonisation and infection of pin sites (Table 1.1). However, the features detailed in "colonisation" could signify irritation or signs of local infection, and the additional criteria detailed under "infection" indicate advanced infection and therefore would not facilitate early diagnosis and treatment. As bacteria may colonise pin sites without causing infection, microbiology culture should be complemented by clinical judgement to determine the bacterial load and differentiate between colonisation and infection.

Table 1.1 Reaction, Colonisation and Infection (Lee-Smith et al 2001)

Reaction	Normal changes that occur after pin insertion Changes in skin colour, warmth, drainage at pin site Changes are expected to subside after 24 hours
Colonisation	Warmth and redness around the pin site, increased drainage, possible pain and positive microbiological culture
Infection	Warmth and redness around the pin site, increased drainage, possible pain, possible pus, pin loosening and increased microbial growth.

There are several assessment tools designed to assess pin sites and identify infection (Saleh and Scott 1992, Checketts et al 1993, Dahl et al 1994, Patterson 2005, Clint et al 2010, Santy et al 2011). Inter-observer reliability when classifying erythema, tenderness and swelling of pin sites often makes assessment subjective and therefore questions the true objectivity of classification tools.

Saleh and Scott's (1992) criteria (Table 1.2) classify infection in terms of treatment rather than quantification of the problem. While it is important to recognise that more severe infection requires more extensive treatment, unless appropriate intervention is implemented, infection will not be eradicated. Insufficient treatment may therefore skew the grading of infection and the effectiveness of this classification.

Table 1.2 Saleh and Scott classification (1992)

Grade	Appearance
0	No problem
1	Responds to local care, for example increased cleansing and massage
2	Responds to oral antibiotics
3	Responds to intravenous antibiotics or pin releases
4	Responds to removal of the pin
5	Responds to local surgical curettage
6	Chronic osteomyelitis

One of the most common PSI grading tools used within research papers is that by Checketts et al (1993) (Table 1.2). While this popular classification tool offers a clear structure to grade the severity of infection, there is a retrospective element to the assessment regarding the response to treatment. Hargreaves et al (2004) used a modified Oppenheim classification, which is similar to that of Checketts et al (1993) although it has not been used to the same extent in subsequent literature.

Table 1.3 Checketts et al (1993) classification

Grade	Appearance
Minor Infections	
1	Slight redness around the pin together with a little discharge and settles with better pin site care
2	Redness in the skin, discharge from the pin site and pain and tenderness in the soft tissues. Settles with improved pin site care and a short course of the appropriate antibiotic which is chosen according to the organism cultured. In almost all cases the organism will be *Staphylococcus aureus*
3	The same as grade 2 but fails to respond with diligent pin site care and the appropriate antibiotic. The affected pin or pins are re-sited and external fixation can be continued
Major infections	
4	There is severe soft tissue infection involving several pins, sometimes with loosening of the pins. Re-sitting of the pins is impossible and external fixation must be abandoned
5	There is radiographic evidence of osteomyelitis in addition to soft tissue involvement. External fixation must be abandoned and the infection then resolves.
6	Occurring after fixator removal following completion of the treatment. The pin track heals initially but subsequently, at intervals, will break down and discharge. The infection will clear with curettage of the pin track in the soft tissue and bone. Will usually show sequestra in the bone with reaction in the adjacent periostium on the proximal cortex

Patterson's (2005) classification tool offers a comprehensive and measurable approach to assessing PSI using observable characteristics such as redness, swelling, and patient discomfort (Table 1.4). The tool has been assessed for content validity, ease of use and objective scoring within clinical practice. Patterson (2005) reported that a score greater than 3 and requiring antibiotics, represented a stage 2 PSI (superficial cellulitis), whereas a diagnosis of a stage 3 PSI (deep infection) required a score greater than 7, treatment with IV antibiotics and/or removal of the pin.

Table 1.4 Patterson (2005) classification

Complications: Pin-site reaction								
Date	Redness	Swelling	Discomfort	Loose	Crusting	Skin/pin tent	Drainage	Total
	1-2-3	1-2-3	1-2-3	Y=20 No=0	1-2	Y=1/No=0	1-2-6	
	1-2-3	1-2-3	1-2-3	Y=20 No=0	1-2	Y=1/No=0	1-2-6	
	1-2-3	1-2-3	1-2-3	Y=20 No=0	1-2	Y=1/No=0	1-2-6	

Redness	**Swelling**	**Loose**	**Tenting**
1= mild erythema<0.5cm	1= mild swelling <0.5cm	20 = Yes	1= Yes
2= mod erythema 0.5-1.0cm	2= mod swelling 0.5-1.0cm	0 = No	0= No
3= severe erythema >1cm out from pin	3= severe swelling >1cm out from pin		

Discomfort	**Crusting**
1= mild w/care intermittent 2= mod guarding against pin care, crisis imminent 3= severe pain reported/observed, combative, constant pain	1 = some ½ or less, surface area of the pin 2 = completely encircles the pin
Drainage	6 week check up: Date...../......./..... Req antibiotic....Yes.....Type.....No Req lancing.....Yes.....No Req pin removal.....Yes.....No Change in protocol.....Yes.....No
1= serous/clear 2= drainage w/colour red, cream, tan, green 6= pus from pin site	

A more simplistic method of classifying PSI was used by Dahl et al (1994) (Table 1.5) which includes 'Grade 0' to indicate a normal appearance and Grade 1 as inflamed. This tool also suggests appropriate treatment although does not use it as part of the classification criteria, making underscoring of PSI less likely to be attributed to inadequate treatment.

Table 1.5 Dahl et al (1994) classification

Grade	Appearance	Treatment
0	Normal	Weekly pin site care
1	Inflamed	Daily pin site care
2	Serous Drainage	Antibiotics
3	Purulent drainage	Antibiotics
4	Osteolysis	Remove pin
5	Ring sequestrum	Debridement

Clint et al (2010) offer a novel grading system which classifies pin sites as 'Good', 'Bad' or 'Ugly', depending on erythema, pain and discharge (Table 1.6). The tool offers a memorable way of assessing and communicating the state of pin sites and has been tested for inter-observer and intra-observer reliability with good effect although has been designed to monitor pin sites rather than to diagnose infection.

Table 1.6 The Good, Bad and the Ugly (Clint et al 2010)

Grade	Erythema	Pain	Discharge
Good	None or minimal (less than diameter of pin)	None	None or minimal serous ooze (not requiring dressing changes)
Bad	Moderate (greater than pin diameter)	On palpation or percussion of the pin	Serous drainage requiring dressing changes
Ugly	Extensive (extending away from pin site)	At rest	Heavy discharge or frank pus

Many of the tools do not take into account patient perception of how swelling or pain has changed, which Santy (2010) argues is major flaw in the assessment tools. Santy et al (2011) subsequently developed the assessment criteria included in Table 1.7 which describes pin sites as 'calm', 'irritated' or 'infected'. The tool however does not specify how many categories are required to formulate a diagnosis of "infection".

Table 1.7 Santy Classification (2011)

	Pain	Redness	Discharge	Swelling	General symptoms
Calm	May be painless. Only mild pain. Reduces after application of fixator.	Often none Sometimes a little Not spreading	Sometimes none Sometimes minor	No Swelling	No other issues
Irritated	Mild to moderate. 'Uncomfortable'	Some redness but not spreading. No hot or taut skin	'Weepy' Begins to weep when it has not before/ increased amount of discharge Remains the same consistency and colour as calm Can be persistent in specific pin sites Sometimes bleeding No odour Dressing changes more often	Swelling around pin site only- not spreading	Associated with: Skin movement around the pin Allergy to antiseptic Irritated with physical activity Itchy (owing to reaction/allergy) Dry flaky skin Does not respond to antibiotics May affect all pins sites or just one or two.
Infected	Severe Sudden Increased intensity Throbbing/stinging Joints nearby may be painful Unable to weight-bear Unrelenting on rest Poor response to analgesia.	Deep red Angry looking Spreading Definite boarders Associated with heat	Increased Change in consistency Thick/ more viscous Unpleasant odour (not always) Change in colour Purulent (not always) Dressing changes much more frequent	Localised swelling around affected pin May spread May be severe	Feeling unwell Fever/pyrexia Taught shiny skin Loss of function/weight bearing Tired/lethargic Disturbed sleep Loss of appetite Responds to antibiotics

Incidence

Reported rates of pin complications vary greatly and range from 7.9% (Battle and Carmichael 2007) to 100% (Hosny 2005; Blum et al 2010). This variability is in part attributable to the lack of universally agreed definitions and classification systems to determine the presence and severity of PSI (Sato et al 2003).

External fixation may pose a considerable infection risk for immunocompromised patients. Norrish et al (2007) compared the rate of PSI in HIV-positive and HIV-negative patients with open fractures. There were no reported differences between the groups with regard to mean number of pins ($p=0.33$), or duration of fixation ($p=0.48$), although the HIV group demonstrated increased severity of infection (Checketts score of 2 or greater) ($p=0.0014$), incidence was not reported.

Mason et al (2005) reported 50% PSI in definitive pelvic external fixators compared to 13% with temporary fixation ($p<0.001$). Mean duration of external fixator was 60 days for definitive external fixation (range 17-113) compared to 8 days for temporary fixators (range 1-20 days). Pin sites were considered infected if a positive microbiological culture was documented and antibiotics used for treatment. Premature removal of temporary fixators was required in 11.5% (6/52) of cases due to infection, compared to 23% (6/26) with definitive fixators. This accentuates the premise that prolonged use of percutaneous devices increases the risk of infection.

Site of infection

In addition to the overall infection rate, depth of soft tissue and type of pin or wire insertion, it is important to establish which anatomical sites are at greater risk of becoming infected. Treadwell (2005) reported 63% of patients undergoing external fixation following osteotomies and tarsometatarsal fusions developed PSI, with all PSI occurring in the proximal pin. Similarly, Lerner et al (2005) observed that all PSI occurred in the femur, upper tibia and upper humerus. In contrast to this Schalamon et al (2007) reported 66% PSI occurred in distal pins.

Once pins become colonized with bacteria there is potential for surrounding pins to become contaminated (Clasper et al 1999) either through poor hygiene, incidental spread or cross-contamination, for example from health care workers. Contamination therefore also requires careful consideration when studying the pattern of PSI.

Causative organisms

Coagulase negative staphylococci (CoNS), micrococci, corynebacteria and *Propionibacterium* spp are the predominant bacteria isolated from skin flora (Guzel et al 2009), although the composition varies across the body depending on many factors such as the amount of sebum, location of sweat glands and moisture (Human Microbiome Project Consortium 2012). While decontamination of the skin is carried out prior to application of external fixation, preoperative skin preparation does not completely remove viable bacteria from the skin (Glen et al 2012).

Bacterial isolates from PSI have been reported by Schalamon et al (2007) to include *S aureus* (33%), *S epidermidis* (22%) and viridans streptococci (17%). Antoci et al (2008) similarly identified the aetiology of PSI as being

predominantly *S aureus (*47%), with smaller numbers of *S epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*. While Lerner et al (2005) reported *S aureus* as being identified in 80% of swabs taken, although other bacterial isolates were not specified.

Effective prevention strategies for PSI therefore need to consider the sites of external fixation, the likely pathogens which may cause infection (Human Microbiome Project Consortium 2012) and appropriate methods to prevent colonisation or infection of pin sites.

Consequence of infection

Pins and wires exposed to the environment are at risk of bacterial contamination, which may then track down the pin towards deep soft tissue and bone. Fluid accumulation around the pin-tissue interface may expedite bacterial spread from the superficial pin site to the medulla before clinical manifestations are present (Clasper 2001b). This has significant implications regarding the potential to develop deep soft tissue infection and osteomyelitis with external fixation, particularly as the presence of a foreign body reduces the minimum inoculum required to cause infection by approximately 10^4 (Elek and Cohen 1957). Osteomyelitis may require prolonged intravenous antibiotic therapy, repeated surgical interventions to re-site pins, debride necrotic areas or implant antibiotic devices to eradicate the infection. In severe cases significant resection or amputation of the limb may be required.

Several bacteria possess adhesins which mediate cell anchorage to implants, or to extracellular proteins such as collagen or fibrinogen present on the implant. The presence of polysaccharide capsule layers in bacteria have also been noted to help cells adhere to biomaterial surfaces (Campoccia et al 2006). A biofilm is a community of bacterial cells which

are attached to a surface and each other, and which are embedded in extracellular polymeric substances that provide structure for the biofilm (Donlan and Costerton 2002). Once bacteria have adhered host defences are unable to prevent further colonisation and biofilm formation at the tissue/implant interface.

Biofilms can go undetected for prolonged periods of time although can act as a persistent source of infection due to the detachment of cells or micro-colonies from the biofilm which cause local infection, or bacteraemia (Donlan 2009). While swabs from pins or exudates can be obtained to identify causative bacteria, it is difficult to identify the presence or size of biofilms while the implant remains in-situ. Biofilms are more resistant to the immune response and to systemic antibiotic therapy (Hetrick and Schoenfisch 2006, Kim et al 2008) due to the reduced bacterial cell growth rate and metabolism within the biofilm. This minimises the effectiveness of antibiotics which target protein synthesis and cell wall synthesis. Thus it may not be possible to eradicate biofilms without removing the affected pin or wire. The prevention of bacterial adhesion and biofilm formation is therefore a principal component in preventing PSI.

1.4 Pin materials

Various combinations of alloys have been evaluated with regard to antimicrobial activity to prevent infection. Combinations include the use of titanium alloys (Shirai et al 2009; Pieske et al 2008), diamond-like carbon (Smith et al 2006), hydroxyapatite containing silver (Shimazaki et al 2010; Chen et al 2007) and silicate-apatite layers (Wang et al 2009). The broad spectrum antibacterial activity of silver against gram positive and gram negative bacteria has also been investigated for the purpose of external fixation (Bossetti et al 2002; Jennison et al 2014; Wickens et al 2012).

However, no significant differences have been identified between SS and silver-coated external fixator pins (Coester et al 2006).

Factors such as ease of pin removal and potential for bacterial adherence are important considerations when contemplating the type of pins to use (Moriarty et al 2010). Surface roughness of implants has been studied often with regard to osseointegration and load transfer from implant to bone. While the aim of external fixation is not osseointegration, bacterial adhesion is a fundamental consideration. Wu et al (2011) compared the differential response of staphylococci and osteoblasts to varying titanium roughness. *S epidermidis* growth was substantially higher on satin and grit-blasted surfaces than on polished or plasma sprayed surfaces. This highlights further uncertainty with studies comparing pin materials as to whether it is the surface topography or material properties which most impacts upon clinical infection rate.

1.5 Pin coatings

Active coatings for implants inhibit bacterial attachment to the implant surface. Polymer coatings such as polyurethane, silicone, and polymethymethacrylate may be used for local antibiotic delivery. Local delivery of antibiotics is dependent on the choice of antibiotics, release rate and restrictions due to chemical and physical properties, such as the ability of the drug to diffuse through the polymer (Hetrick and Schoenfisch 2006). Delivery systems should provide effective doses continually to the target site (Wu and Grainger 2006) and offer therapeutic drug release over prolonged periods (Liu et al 2002). If antibiotic delivery falls below the MIC, bacteria may attach to the device and form biofilms (Ziberman and Elsner 2008).

Tobramycin-impregnated polymethylmethacrylate pin sleeves were trialled by Voos et al (1999) using a goat model. Treated pins did not show any bacterial growth at 48 hours and did not display signs of infection at day 16. Pin sleeves were fitted following pin insertion so potentially could be replaced as required. As this study ran for only 16 days it is not clear if this method would be effective for longer periods or if frequent changing of pin sleeves would be required to maintain effectiveness.

Gentamicin-coated polyurethane sleeves designed to sit flush against the bone and sit at least one cm above the pin entry site were assessed by Forster et al (2004). Elution testing with *S epidermidis* demonstrated sustained release of antibiotics above MIC (4µg/L) for up to 20 weeks. Sleeves were designed to be inserted during the placement of pins and remain in-situ until frame removal. No details were given about the feasibility of replacing the sleeves if fixation were required in excess of 20 weeks.

Antibiotic coatings have been studied using immersion in antibiotic solutions (Stiger et al 2002), surface-induced mineralisation (Campbell et al 2000), chitosan (Greene et al 2008) and pexiganan, an antimicrobial peptide (Chou et al 2010). The use of biodegradable coatings and polypeptide nanofilms on implants has also been studied (Basak et al 2009; Li et al 2010). However, studies have demonstrated effectiveness only over a matter of hours or days and have yet to demonstrate efficacy over prolonged periods of time similar to the duration of an external fixation. Feasible methods of reactivation or replacement of coatings once the antibiotic concentration falls below MIC therefore requires careful consideration.

1.6 Pin site management

The skin constitutes a major source of organisms responsible for wound infection (or PSI). A number of skin cleansing products are available such as chlorhexidine, povidone-iodine, ethanol and hydrogen peroxide, but careful consideration is required to establish the effective balance between decolonisation and maintaining tissue viability of the area. Chlorhexidine has bactericidal properties which are not affected by the presence of body fluids, and which can be further increased when used with an alcohol base rather than an aqueous base (Reichmann and Greenberg 2009). Octenidine dihydrochloride is also a broad spectrum topical antimicrobial agent which is effective against gram positive and gram negative bacteria and may be considered an alternative to chlorhexidine (Krishna and Gibb 2010), however it has not yet been trialled in pin site care. There is insufficient evidence to support use of topical silver preparations to prevent wound infections (Storm-Versloot et al 2010), although this has not been tested specifically in relation to preventing PSI.

There is currently insufficient evidence for any particular strategy of pin site care to reduce the incidence of PSI (Lethaby et al 2013). Many studies are retrospective cohorts which lack randomisation or control groups, while others contemplate numerous variables within the same study. There are a small number of randomized studies of good methodological standard, although these address different aspects of care, e.g. cleansing (Henry, 1996), frequency of care (W-Dahl et. al. 2003), or choice of products (Yuenyongviwat and Tangtrakulwanich 2011). This makes comparison of data and population groups difficult.

In an attempt to standardise care and promote best practice the Royal College of Nursing (RCN) issued guidelines based on current clinical consensus (Timms et al 2011). These are summarised in Table 1.8. The British consensus group consisted of specialist practitioners working in the field of limb reconstruction and external fixation. The consensus document was developed based on delegates' opinions following a series of presentations and discussions (Timms et al 2011). The researcher was part of the consensus group, although did not contribute to the data analysis or published report.

Table 1.8 RCN consensus recommendations (2011)

- Pin sites should be cleansed with a solution of chlorhexidine in alcohol.
- If chlorhexidine in alcohol is contraindicated saline should be used for cleansing
- Cleansing should be performed using a non-shedding material.
- Pin sites should be cleansed and dressed every seven days.
- Dressings should be changed more frequently if:
    - there is copious discharge
    - the dressing is wet
    - infection is suspected
- Pin sites should be covered at all times with an initially sterile dressing
- The dressing should be constructed of a non-shredding material which keeps moisture and exudate away from the wound.
- Light compression should be applied to the wound using a bung, clip or other device
- Patients should not be allowed to bathe but may shower immediately prior to dressing changes

(Timms et al 2011)

Dressings

The use of dressings in pin-site management is poorly researched and affords great variation in clinical practice (Santy and Newton-Triggs 2006; Lethaby 2013). Timms et al (2011) advised that pin sites should remain dressed throughout the entirety of treatment to prevent ingress of bacteria, in parallel with recommendations for percutaneous insertion sites (Pratt et al 2007). The RCN consensus document also considered crusts and scabs to form a natural barrier to prevent PSI, as described by Britten et al (2013). However, quality evidence on pin site dressings is sparse and a Cochrane review identified no studies specifically focusing on whether or not to use dressings for pin sites (Lethaby et al 2013).

Biopatch is a chlorhexidine-impregnated sponge, commonly used for intravenous insertion site dressings, and has demonstrated a significant reduction in PSI when used with fixator pins (25% v 0%, p=0.047) (Wu et al 2008). However inconsistent results are evident as Egol et al (2006) reported no significant differences in pin related complications between dry dressing and Biopatch (18% v 19%). In a prospective study of 100 patients with femoral nerve catheters Schroeder et al (2012) reported no significant reductions in colonisation or infection rates (6.6% Biopatch v 4.3% non-Biopatch). Similarly, Arvaniti et al's (2012) multicentre randomised control trial reported no significant difference in central venous catheter related infections between non-antimicrobial catheters (5.8%), chlorhexidine-impregnated sponge (4%) and silver impregnated catheters (4.4%) (p=0.58). Weichman et al (2015) also reported no statistical differences in infection using Biopatch at drain sites (6.2% Biopatch v 7.4% control, p=0.42). Due to the inconsistent results reported in the literature with chlorhexidine-impregnated sponge alternative preventative strategies against PSI are required.

1.7 Antimicrobial impregnated device

The use of medical grade silicone impregnated with antimicrobials has proven effective at reducing infection rates in neurosurgical shunts (Bayston 1997) without any hypersensitivity or toxicity problems (Bayston 2007a). This technology has also demonstrated prolonged antimicrobial activity with peritoneal catheters, with the expectation that this will reduce infection rates in future clinical trials (Bayston 2009).

Clinical studies using antimicrobial impregnated catheters have demonstrated significant reductions in cerebrospinal fluid shunt infection rates (Pickard et al 2015). Studies by Klimo et al (2014), Raffa et al (2015) and Edwards et al (2015) also highlight the effectiveness and potentially cost-saving benefit of this impregnation technology in clinical practice.

It is proposed that carefully selected antimicrobials can be impregnated into silicone discs designed to fit around the pin or wire as a collar at the skin-pin interface. This would provide an area of antimicrobial activity which is designed to prevent infection from organisms commonly isolated at pin sites. Although previous studies of external ventricular drainage shunts and peritoneal catheters have impregnated the whole device to reduce the risk of infection, silicone collars could be easily replaced if the treatment period exceeds the duration of antimicrobial activity, thus offering a more practical solution than replacing antimicrobial pins or wires, or reapplying antimicrobial coatings.

It is hypothesised that the use of an antimicrobial collar would prevent the pin site from becoming colonised and consequentially developing a PSI. Selection of antimicrobials therefore requires careful consideration of the antimicrobial spectrum, safety in clinical use as well as the stability and physico-chemical characteristics (Bayston et al 2004). In addition to the antimicrobial properties and resistance factors which need to be considered, the molecules need to be able to migrate through the silicone polymer (Bayston et al 1989), and be heat-stable so that the collar remains active after autoclaving.

Both gentamicin and vancomycin offer appropriate antimicrobial coverage against potential PSI pathogens. However, their insolubility in chloroform renders them inappropriate for use with the selected impregnation process (Fisher 2011, FDA 2008). Antimicrobials considered for impregnation included chloramphenicol, ciprofloxacin, clindamycin, fusidic acid and trimethoprim, as heat stable antibiotics. As the adverse effects of chloramphenicol include bone marrow suppression, hypersensitivity and neurotoxic reactions, this was not selected for impregnation.

Resistance to antibiotics can be easily induced with exposure to single drugs, but, with the appropriate use of combination therapy resistance is uncommon (Munckhof et al 2004). The combination of trimethoprim and clindamycin was previously tested by Bayston et al (1989) and reported not to be compatible with the impregnation process. Similarly, the experimental work by Bayston et al (1989) also identified that the antimicrobial combination of rifampicin and fusidate was less effective on in-vitro testing than the clindamycin and rifampicin combination.

Rifampicin, clindamycin and triclosan were therefore selected for use in the antimicrobial collar due to their combined antimicrobial properties against gram positive and gram negative bacteria, ability to migrate through cross-linked silicone polymer and heat-stability allowing sterilisation by autoclaving as identified by previous studies by Bayston et al (1989) and Traub and Leonhard (1995).

Other antimicrobial combinations may have been selected for use in the antimicrobial collar. For example octenidine dihydrochloride is an alternative product that could be substituted for triclosan, but, as it offers a shorter duration of activity than triclosan (Fisher 2011) it was not selected for impregnation.

Rifampicin

Rifampicin belongs to the rifamycin group. It is highly active against staphylococci (Barriere 2006), which are the commonest cause of PSI and can be used as an adjunct to treat Methicillin resistant *S aureus* (MRSA) (MERCK Manual 2014). Rifampicin also has broad antimicrobial properties against other gram positive organisms (Morris et al 1993).

Rifampicin binds to bacterial RNA polymerase, inhibiting the RNA synthesis responsible for DNA transcription (Wehrli 1983). Bacterial resistance is common with rifampicin monotherapy due to the single step mutation in the β subunit of bacterial RNA polymerase which renders the bacteria resistant (Barriere 2006; Goldstein 2014). However, due to the low toxicity of rifampicin it is frequently used for combination antimicrobial treatment, often with improved treatment outcomes (Forrest and Tamura 2010).

Clindamycin

Clindamycin belongs to the lincosamide group of antibiotics and can be used for treatment of gram positive cocci (including MRSA), which are common causes of skin and soft tissue infections (Dhanalakshmi et al 2012, MERCK Manual 2014). Clindamycin can also used for anaerobic infections (Bartlett et al 1972) and is a useful alternative in penicillin allergies (Prabhu et al 2011).

Clindamycin inhibits ribosomal translocation and protein synthesis by binding to the 50S rRNA of the bacterial ribosome sub-unit (MERCK Manual 2014). Enterococci and gram negative bacilli are characteristically resistant to clindamycin due to active efflux mechanisms (Singh et al 2002, Merck Manual 2014). Inducible resistance has been reported in bacterial isolates which were sensitive to clindamycin, although resistant to erythromycin (Yilmaz et al 2007).

Triclosan

Triclosan is a synthetic bisphenol compound which is active against gram positive and gram negative bacteria (Suller and Russell 2000), also possessing some antifungal properties (Bhargava and Leonard 1996). Triclosan has been used for over 40 years as a general antibacterial and antifungal agent in many products ranging from toothpastes and soaps to plastic kitchenware and carpets (Levy et al 1999).

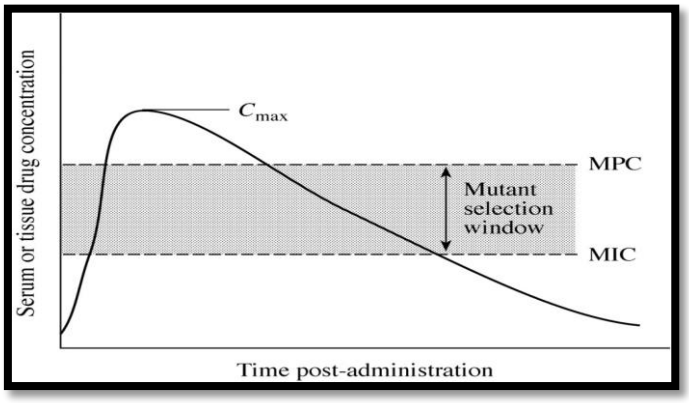
Triclosan inhibits fatty acid synthesis by binding to the bacterial enoyl-acyl carrier protein reductase enzyme which is coded by the gene *fabI* (McMurry et al 1998). Mutations in, or over-expression of *fabI* prevents the inhibition of fatty acid synthesis. The presence of efflux pumps in bacteria such as *Pseudomonas aeruginosa* can also make bacteria intrinsically resistant to triclosan (Chuanchuen et al 2003). There is an increasing number of reports detailing triclosan resistance (Ciusa et al 2012; Bayston et al 2007b; Suller and Russell 2007), although this is not necessarily associated with increased virulence (Latimer et al 2012; Bayston et al 2007b).

It is anticipated that the combined use of clindamycin, rifampicin and triclosan in collars placed at the pin site will provide antimicrobial protection against gram positive and gram negative bacteria and prevent PSI in patients with external fixation.

Antimicrobial resistance

A concentration window exists in which bacterial resistance mutations may be selectively increased. This occurs between the lowest concentration of antimicrobial that inhibits the growth of susceptible cells (minimum inhibitory concentration - MIC) and the mutant prevention concentration (MPC), which blocks the growth of the least susceptible single step mutant (Drlica 2003). This is referred to as the mutant selection window (Figure 1.5). Using antimicrobial concentrations outside of this window will restrict selective enhancement of mutant strains (Drlica 2003).

Figure 1.5 Mutant selection window and antimicrobial resistance

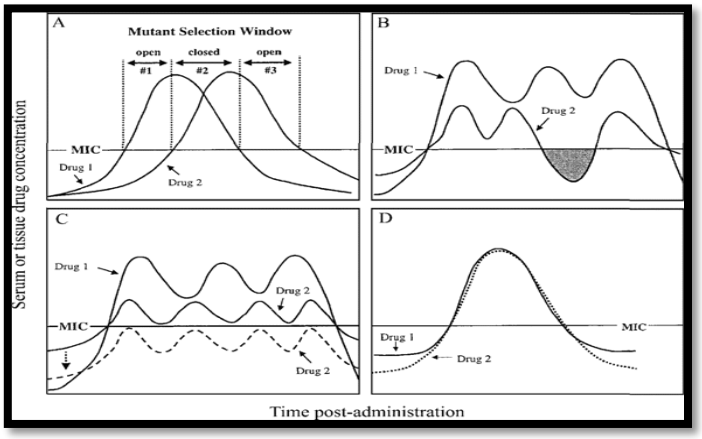


Pharmacodynamic depiction of the mutant selection window. A hypothetical pharmacokinetic profile is shown in MIC and MPC are arbitrarily indicated. Double-headed arrow indicates the mutant selection window. (Dlica 2003)

The combined use of appropriate antimicrobial agents with similar pharmacokinetic profiles above the MIC prevents bacterial adaptation by minimising the mutant selection window (Figure 1.6). This is referred to as the dual drug principle (Zhao and Drlica 2001).

Conventional systemic delivery of antibiotics has the disadvantages of systemic toxicity and associated liver and renal complications as well as poor penetration into soft tissues, ischaemic and necrotic tissue (Price et al 1996). Local antibiotic therapy however, has the advantage of high local concentrations over a prolonged duration without systemic toxicity (Forster et al 2004; Zalavras et al 2004). Local antimicrobial therapy also permits focused selection of antibiotics directed towards specific pathogens, and can be targeted towards treatment or prevention of infection. The effectiveness of local delivery systems are however dependent on the rate and manner in which drugs are released.

Figure 1.6 Dual drug principle (Zhao and Drlica 2001)



A) Mutant selection windows open due to insufficient overlap of pharmacokinetic profiles

B) Mutant selection window open due to fluctuation in antibiotic treatment.

C) Mutant selection windows open due to fluctuation in antibiotic concentration

D) D Mutant selection window is closed as both compounds have identical pharmacokinetics above the MIC (Zhao and Drlica 2001)

Clindamycin and rifampicin concentrations were selected based on previous experimental work by Bayston et al (1989) which demonstrated that hydrocephalus shunt catheters impregnated with rifampicin and clindamycin using a 0.2% solution were able to resist consecutive bacterial challenges over a period of 28 days of constant perfusion using an in-vitro model. Resistance was identified using lower antimicrobial concentrations. Further work using peritoneal catheters impregnated with 1% triclosan, 1% trimethoprim and 0.2% rifampicin solution (w/v) identified antimicrobial activity which continued for 280 days (Bayston et al 2009). This concentration was therefore selected for triclosan.

Due to the potential for bacterial resistance to develop it is essential that new devices and antimicrobial combinations are tested rigorously prior to clinical use to establish the duration of antimicrobial activity against target organisms, and identify evidence of resistance following prolonged exposure to antimicrobial materials. It is also important to consider the manufacturing process, and how this may influence product cost and environmental impact.

1.8 Patient and public involvement

As well as the antimicrobial considerations, the collar needs to be available with different centre diameters to ensure that the collar fits the circumference of the pin. It is also important that the collar is in contact with the skin surface to ensure maximum antimicrobial effect. To ensure patient compliance with the use of an antimicrobial collar it is important that the collar is easy to use, non-irritant and acceptable to both patients and clinicians. With an appropriate design it is anticipated that the collars will allow for easy removal and replacement to allow surveillance of pin sites or perform routine care such as cleansing.

Patient and public involvement (PPI) enables researchers to gain insight into service user needs and the issues of importance to health care users. Active involvement of service users and carers is an important strategy in developing effective research (DoH 2005), understanding how novel interventions such as the antimicrobial collar will meet service user needs and identifying potential problems, for instance with the product or with recruitment and retention before trials commence. Different approaches for engaging people in consultations and partnerships should be considered for different purposes and endpoints within research (Oliver et al 2008). This can range from qualitative approaches to elicit ideas and opinions, such as

focus groups and one-to one interviews, to more quantitative approaches such as questionnaires (Mullen 1999).

Engaging with health care workers is also key to ensuring their support throughout the research process. Understanding the attitudes, knowledge and beliefs of health care professionals and how these influence clinical practice is an important element to understanding how the proposed research/product will fit in to current practice (Parahoo 2006).

Patient evaluations

Traditional outcome measures of mortality and morbidity remain important markers although are often unhelpful when assessing the broader impact of trauma or disease, and the impact of health care interventions. This has resulted in an increased emphasis on measuring the quality of care and health related quality of life (HRQoL) (Haywood 2006).

Participant feedback is an important aspect of product design, particularly with regard to ease of use, comfort, general aesthetic properties and practicalities of the antimicrobial collar. This is also an important part of quality assurance to determine fitness for purpose and will feed into the final design of the antimicrobial collar from the current prototype.

Well-developed outcome measures are a key source of evidence regarding the patient experience. Patient evaluations can be used to distinguish between the process and outcome to develop services and products in a holistic manner. Different aspects of patient experience need to be considered as part of the evaluation and feedback process.

Patient-reported outcome measures (PROMs) can gather information on the effectiveness of care and patient expectations. PROMs are an important aspect of outcome measures, as these may differ fundamentally from

surgeon/clinician opinion. Monitoring PROMs can ensure services and innovations align with patient expectations (DoH 2010) and can assist with service and product improvement. As such it is important to develop the process of collecting information on the effectiveness of care, as perceived by patients (HSCIC 2014).

Various standardised PROMs are available as indictors of general health, disease impact or extremity function (Calfee and Adams 2013), although these do not adequately capture the full impact of injury on health and well-being (Hoffman et al 2014). No PROMs specifically designed for patients treated with external fixation were identified as part of the literature review.

Patient experience is also an important component of healthcare quality and is a central outcome alongside clinical effectiveness and safety (de Silva 2013). Quality of care, compassion, dignity and respect can only be improved by analysing patient satisfaction with their own experiences (DoH 2010). There are currently no patient-reported experience measures (PREMs) for patients with external fixator devices. It is therefore important to develop a set of PREMs for these patients which puts patient experience and outcome as a central metric for quality improvement (DoH 2010). However, before a valid tool can be devised and implemented, it is important to identify what patients view as important experience measures.

1.9 Research aims and hypothesis

The purpose of this study is to determine the feasibility of silicone collars impregnated with carefully chosen antimicrobials in preventing PSI in patients with external fixation. This research will identify current practices for pin site care and compare an antimicrobial impregnated silicone collar with standard care to determine the feasibility of the novel intervention in preventing pin site infection.

The research questions posed are:

1) What are current pin site management techniques?
2) Which bacteria are commonly associated with infected and colonised pin sites?
3) Can we generate in-vitro data to indicate whether antimicrobial–impregnated collars can prevent or reduce PSI?
4) Can the antimicrobial collars prevent bacterial resistance during use?
5) Is the collar acceptable to patients with external fixators?

The objectives of this study are to:

- Identify current regimens for pin site care.
- Establish the reliability of selected clinical assessment tools for pin site infection.
- Identify and evaluate bacteria colonising pin sites.
- Identify and evaluate bacteria present in pin site infection.
- Determine the effectiveness of antimicrobial collars against bacteria isolated from cases of PSI by means of in-vitro testing.
- Determine the effectiveness of antimicrobial collars in preventing bacterial resistance in the laboratory setting.
- Determine the effectiveness of the antimicrobial collar in preventing colonisation of the pin track using an in-vitro model.
- Determine if there is a difference between the antimicrobial qualities of serial impregnated discs using the same impregnation solution using in-vitro testing.
- Conduct a feasibility study to evaluate the safety and acceptability of the antimicrobial collars to participants.
- Identify patient outcome measures and patient experience measures for patients with external fixation devices.

The hypotheses of this research are:

1) The use of an antimicrobial-impregnated collar will show in-vitro evidence of its ability to prevent or reduce the occurrence of PSI.
2) That the antimicrobial collar is acceptable for use by patients.

Chapter 2 Methods

2.1 Survey of current pin care regimes

In order to explore current pin site management strategies and identify the potential market for the antimicrobial collar, a questionnaire was devised. Questions focused on topics outlined in UK consensus guidelines (Timms et al 2011) to ensure content validity. No distinction was made between the type and site of external fixator, or between pins and wires to avoid over-complicating the questionnaire and risking reduced response rate.

An electronic questionnaire approach was selected (Survey Monkey) due to the ability to reach respondents from around the world, at a relatively low cost (Reitz and Anderson 2013). Additional benefits of an internet-based survey include fewer errors with data input (Hoonakker and Carayon 2009) and the relative speed with which surveys can be disseminated, completed and analysed (Sheehan and McMillan 1999). Disadvantages to this method include difficulties in selecting samples that adequately cover the target population (Reitz and Anderson 2013), and potentially lower response rates (Nulty 2008).

The survey was peer-reviewed by senior academics, orthopaedic surgeons and senior orthopaedic nurses. One question was revised following feedback on the clarity of instructions. The final survey is included in Appendix 1.

A convenience sample was identified through:

- Online searches for professionals within the speciality
- Author contact details from relevant papers
- Special interest groups – Australian & New Zealand Orthopaedic Nurses Association (ANZONA), British Limb Reconstruction Society (BLRS); Society of Orthopaedic and Trauma Nursing (SOTN)

One thousand three hundred and fifty-seven invitations were sent by email. The survey was left open for 100 days to permit adequate time to respond. Although a non-probability sample restricts the generalisability of findings, a purposive convenience sample provides greater control over the sample composition and enables the questionnaire to be directed to appropriate clinical groups (Parahoo 2006).

Data were analysed using SPSS statistical package (Version 22). Chi-square tests were used to identify significant differences in practices between geographical regions and professional groups. Confidence intervals were calculated to determine the extent that practices in the UK conform to current consensus guidance (Timms et al 2011).

2.2 Assessment tools

To enable a thorough assessment of pin sites in the study three tools were chosen to assess for 'clinically' infected sites. These included Checketts et al (1993) due to its popularity in research literature, Patterson (2005) due to the quantitative assessment process and Santy et al (2011) as it includes variables associated with irritated and infected pin sites. To determine inter-observer agreement of these tools eleven nurses independently scored ten images of pin sites using each of the assessment

criteria. These assessments were repeated two weeks after the initial assessment.

Intraclass correlation was calculated for each tool calculating for absolute agreement. Test-retest data was analysed with two-way multiple measures analysis of variance (ANOVA). All calculations were performed using SPSS.

2.3 Identification and evaluation of bacteria colonising pin sites

In order to effectively select antimicrobial agents to prevent PSI it is important to ascertain which bacteria commonly colonise pin sites. Swabs were taken from clinically non-infected pin sites as assessed using three clinical scoring tools (Checketts et al 1993, Santy 2011 and Patterson 2005).

Audit can be defined as assessing the level of service provided against a set of predetermined standards whereas service evaluation is undertaken to define or judge current service (Health Research Authority 2009). Neither service evaluation nor audit involve intervention or change to the standard service being delivered as occurs with research. As the identification of bacteria colonising pin sites did not involve change to the standard service being delivered, and there were no predetermined standards for assessing bacteria colonising pin sites, this work was classified as service evaluation.

Bacteria were isolated and characterised using the following standard microbiological techniques:

- Gram stain
- Catalase (hydrogen peroxide – Oxoid, Basingstoke, UK)
- Oxidase test (Oxoid, UK)
- API micro-organism identification tests (bioMérieux, Basingstoke, UK)

The identified samples were stored in cryobank vials (Mast Cryobank, Bootle, UK) at -20°C for future use.

2.4 Identification and evaluation of bacteria from pin site infections

An important element of preventing PSI is ascertaining which bacteria are commonly associated with PSI. By contrasting bacteria isolated from PSI and isolates from clinically non-infected sites it may be possible to predict which bacteria are more likely to cause infection.

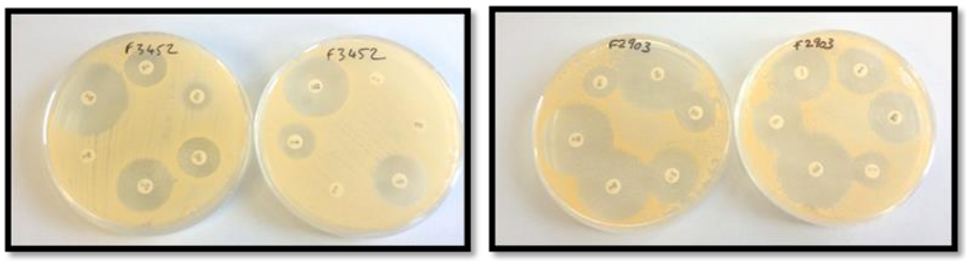
Validated assessment tools (Checketts et al 1993, Santy 2011 and Patterson 2005) were used to identify clinically infected pin sites and swabs were taken for microbiology culture and sensitivity testing. Bacterial samples obtained were isolated, characterised and stored using standard microbiological techniques as specified in Section 2.3.

Multivariate analysis of variance was calculated using SPSS to identify differences between the multiple isolates. Bonferroni adjustments were included for further univariate analysis. Discriminate function analysis was also carried out using SPSS to determine predictor variables.

Antimicrobial sensitivity

Isolates identified from PSI's were tested for antimicrobial susceptibility by growth on Iso-Sensitest agar (ISA, Oxoid) using a modified Stokes diffusion method with commercially prepared discs (Oxoid). Blood agar plates were used for corynebacteria. Plates were seeded with a bacterial suspension of 0.5 McFarland's standard (spectrophotometer absorbance reading of 0.08 - 0.13 turbidity, 490nm) as described by the British Society for Antimicrobial Chemotherapy (BSAC 2015). Antibiotic discs (penicillin, tetracycline, chloramphenicol, erythromycin, trimethoprim, gentamicin, clindamycin, rifampicin, vancomycin, fusidic acid, teicoplanin and ciprofloxacin) were placed on the plates and incubated for 24 hours at 37°C. Zones of Inhibition (ZoI) were measured for each disc using digital callipers (Figure 2.1) and results were documented using antibiogram profile sheets (Appendix 2). Sensitivity was determined using BSAC staphylococci breakpoints for each antibiotic (BSAC 2015).

Figure 2.1: Antibiogram plates for F3452 and F2903



Methicillin susceptibility was determined by growth on ISA containing 4% polyvinyl pyrrolidone (Sigma-Aldrich, Dorset, UK), with and without methicillin 12µg/mL (Bayston 1978). Corynebacteria were tested using blood agar plates and diffusion methods with commercially prepared discs.

Triclosan sensitivities were determined using agar incorporation on ISA with 1.28 mg/L, 0.08mg/L and 0.01mg/L concentrations. Corynebacteria were tested using disc diffusion, with 30 µL of 1.28mg/mL triclosan on sterile discs placed on blood agar plates seeded with 0.5 McFarland standard bacterial suspension and incubated for 24 hours at 37°C

Anaerobe sensitivities for clindamycin and rifampicin were determined using E-test strips placed on agar plates seeded with a fresh bacterial suspension of 0.5 McFarland's standard and agar incorporation methods were again used for triclosan sensitivity testing. Clindamycin sensitivity was determined using BSAC (2015) breakpoints for anaerobes, and *C difficile* for rifampicin.

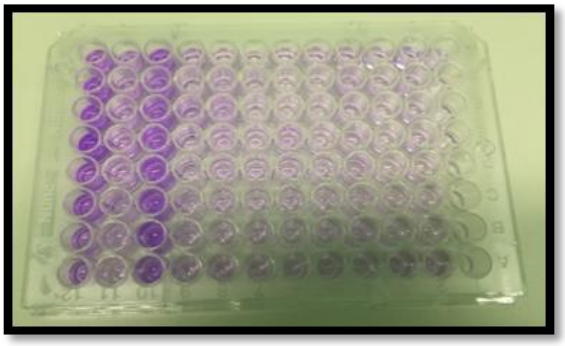
Biofilm identification

Biofilm development might indicate which bacteria have the potential to cause persistent and recurrent infections and can be used as surrogate indicator for virulence and pathogenicity. The crystal violet microtitre assay was used for biofilm biomass quantification (Pitts et al 2003) with interpretation according to Stepanović et al (2000).

Bacterial isolates obtained from PSI were tested for biofilm development. Bacteria were inoculated into 20mL Tryptone Soya Broth (TSB, Oxoid) and incubated using an orbital shaker set at 37°C, 200rpm for four hours. Optical density (OD) was standardised at 0.6-0.7 at 490nm using a Genway spectrophotometer and 200µL of each strain was added to 8 wells of a 96 well microtitre plate and incubated for 24 hours at 37°C. Wells were aspirated and washed twice in phosphate buffered saline (PBS) before fixing with 150µL methanol. After drying, crystal violet stain (2%) was added to each well (150µL) for 15 minutes and the plates rinsed under running water, and then left to air-dry. 150µL methanol was added to each

well for 30 minutes before 100µL was transferred to a fresh microtitre plate (Figure 2.2). Optical density was read using a plate reader at 490nm. TSB was used as a control medium.

Figure 2.2 Crystal violet microtitre assay indicating increased biofilm production of strains tested in column one and three.



The mean value of the wells for each sample was calculated. The cut-off OD (OD_c) for the microtitre plate test was defined as three standard deviations above the mean OD of the control. Based on the OD, results were interpreted using the Stepanović classification listed in Table 2.1. Adherence of bacteria to the bottom and walls of the wells was indicative of biofilm formation.

Table 2.1 Biofilm classification (Stepanović et al 2000)

$OD \leq OD_c$	Non-adherent
$OD_c < OD \leq 2 \times OD_c$	Weakly adherent
$2 \times OD_c < OD \leq 4 \times OD_c$	Moderately adherent
$4 \times OD_c < OD$	Strongly adherent

Anaerobic isolates were incubated in 20mL anaerobic basal broth (ABB) for 48 hours in an anaerobic cabinet at 37°C. OD was standardised as above and samples incubated for a further 48 hours in the anaerobic cabinet before processing and reading using the above mentioned methods.

2.5 Impregnation process

Collars were cut from 2mm thick medical grade silicone (Goodfellow, Huntingdon, UK) using a shape cutter. Centre holes were made using appropriate sized cutters to accommodate external fixator pins and wires. Collars were impregnated using 0.2% clindamycin, 1% triclosan and 0.2% rifampicin solution (w/v), adhering to the protocol in Appendix 3. Collars were sterilised by autoclaving at 121°C for 15 minutes before use.

Reuse of solution for re-impregnation

As re-use of solutions would decrease manufacturing costs and reduce environmental impact with the disposal of waste products, the feasibility of reusing the antimicrobial solution for further impregnations was tested using serial impregnations. Following the initial impregnation process, four subsequent batches of collars were impregnated using the original chloroform solution in the same manner as Batch one. Fifteen collars were impregnated for each batch for the purpose of further in-vitro testing.

Samples (1mL) of antimicrobial solution were obtained for high performance liquid chromatography (HPLC) analysis before impregnation of each batch. After impregnation the collars were removed and a further 1mL sample was obtained for HPLC analysis. The antimicrobial solution volume was then made up to 100mL with chloroform and another 1mL sample taken for HPLC. This process was repeated for each serial impregnation.

2.6 In-vitro testing of collars

It is important to establish the effectiveness of the novel antimicrobial collar in controlled environments prior to clinical trials. The application of the patented technology has proved successful in other clinical settings (Bayston and Lambert 1997; Sciubba et al 2005), although still requires rigorous testing in the circumstances modelled with PSI. The antimicrobial collar aims to prevent colonisation of the pin site and subsequent infection without the emergence of bacterial resistance.

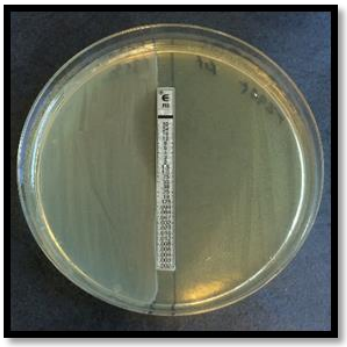
By investigating the collar using in-vitro methods the collars can be evaluated in terms of effectiveness, and predicted clinical outcomes. A number of different techniques were used to evaluate the collars in reducing bacterial counts.

Identification of test bacteria

Clinical strains identified from PSI were selected for in-vitro testing of the antimicrobial collar. Strains were selected based on their commonality in the PSI evaluation and antimicrobial profile that was representative of the remaining organisms. Due to the small number of gram negative bacteria identified from the clinical evaluation, a strain of *E.coli* was selected from the freezer bank.

MIC levels were determined for clindamycin and rifampicin using E-test strips applied to ISA plates seeded with 0.5 McFarland standard bacterial suspension and incubated for 24 hours at 37°C. Blood agar plates were used for corynebacteria. The MIC was defined as the point at which the bacterial growth met the E-test strip (Figure 2.3).

Figure 2.3 Rifampicin E-test to determine the MIC for F3592 (left) and F2904 (right)



Triclosan MICs were obtained using microtitre assays. A 96 well microtitre plate was used containing 100µL TSB per well and 10 µL of test bacteria (0.5 McFarland Standard). Triclosan concentrations ranging from 6.4 mg/L to 0.00625mg/L were added (100µL). A control well without triclosan was included. Each stain was tested in triplicate. Plates were incubated at 37°C and results read at 24 hours.

Inducible resistance to clindamycin may occur in bacterial strains where the *erm* gene is present and where there is resistance to erythromycin (Lewis and Jorgensen 2005). Inducible resistance was tested using a disc diffusion method using 15 µg erythromycin disc placed 1.5cm away from a 2 µg clindamycin disc on a blood agar plate seeded with 0.5 McFarland standard bacterial suspension (BSAC 2015). The plates were incubated at 37°C and results read at 24 hours. Clindamycin resistance is indicated by a flattening of the ZoI around the clindamycin disc (Fieblkorn et al 2003).

Serial plate transfer test

Serial plate transfer test (SPTT) was used to establish the duration of the antimicrobial activity of impregnated collars against target organisms under static conditions (Bayston 1981). SPTT can also be used to identify bacterial resistance following prolonged exposure to antimicrobial materials as noted by the reduction in ZoI or bacteria immediately in contact with the antimicrobial biomaterial (Bayston et al 2009).

ISA plates (20mL) were seeded with bacterial suspensions of 0.5 McFarland's standard. Blood agar plates were used for corynebacteria. Antimicrobial and control (non-impregnated) collars were autoclaved and applied to the centre of the seeded plates using sterile forceps and incubated for 24 hours at 37°C. The ZoI around the discs were measured with digital callipers and recorded. The discs with a ZoI were removed and placed on to freshly seeded plates, ensuring that the same side of the disc was in contact with the agar. All tests were carried out in triplicate.

SPTT tests were also carried out using individually impregnated discs to determine the spectrum and activity for single agents. Bacterial strains F2903 (*S aureus*) and F1693 (*E coli*) were selected based on sensitivity profiles. Discs were impregnated using solutions of 0.2% clindamycin, 0.1% clindamycin, 0.2% rifampicin, 0.1% rifampicin, 1% triclosan and 0.5% triclosan.

Time to Kill Assay (tK100)

Due to the decreased antimicrobial susceptibility of attached bacteria compared to planktonic (Williams et al 1997), it is important to evaluate the time taken to kill bacteria attached to the collar surface. The term tK100 refers to the ability of the antimicrobial agents to kill 100% of the attached bacteria (Fisher et al 2015). The tK100 method was selected due to previous use with similar products (Bayston et al 2010; Bayston et al 2009; Bayston 2004), and validity in measuring the activity of the antimicrobial collar against bacteria which have adhered to the biomaterial. Alternative methods of quantifying bacteria include microscopy, vortexing the product in solution and plating on to blood agar, or rolling the surface across an agar plate (Boersma et al 2008), although these methods were not considered as effective at tK100 for evaluating attached bacteria.

It is important to determine the concentration of TSB necessary to enable survival of the bacteria attached to control discs without allowing planktonic multiplication, which would invalidate the assay (Fisher et al 2015). The concentration was determined by experimentation for each isolate to identify the correct concentration required to maintain bacterial counts on the control discs consistently across 72 hours. TSB concentrations are listed in Table 2.2

Several colonies of the test isolates were placed in 20mL universal containers containing TSB and grown to early log phase in an orbital shaker set at 37°C, 200rpm for four hours. Universals were centrifuged for 15 minutes at 3000 rpm and re-suspended using the appropriate percentage TSB. Optical density was standardised at OD 0.7-0.8 at 490nm using a Genway spectrophotometer, approximately 10^8 cfu/mL. Suspensions were then diluted to 10^6 cfu/mL and 1mL added to 1.5 mL

Eppendorf. Antimicrobial discs (3mmx2mm) were immersed in the bacterial suspension and incubated at 37°C for one hour to allow attachment to occur. The discs were then rinsed in 1mL of appropriate concentration TSB to remove any non-adherent bacteria and placed in to fresh TSB.

Table 2.2 TSB concentrations for TK100 test strains

Freezer number	**Bacterial Isolate**	**% TSB**
F1693	*E coli*	0.5
F2903	*S aureus*	2
F2905	*Corynebacterium group G*	1
F3412	*Corynebacterium jeikeium*	100
F3451	*S epidermidis*	4
F3501	*Corynebacterium macginleyi*	100
F3592	*S aureus*	1

Attached bacteria were removed from the discs at 0, 24, 48 and 72 hours by placing the Eppendorf in to a sonicator for 5 minutes set at 50 Hz (Ultra Wave Ltd, UK). 200µL of the bacterial solution were spread on blood agar plates and incubated for up to 72 hours at 37°C. Surviving bacteria were counted. Control (non-impregnated) discs were tested in the same manner. All tests were performed in triplicate.

Pin track bacterial migration assay

A pin track model was used to simulate the clinical environment and determine the effectiveness of the antimicrobial collars in preventing bacteria tracking down the pin or wire under static conditions. The pin track model can also identify bacterial resistance following prolonged exposure to the antimicrobial materials.

Method development

ISA was made to 75% strength to allow visibility of the pin/wires. 200mL of ISA solution was poured in to Duran bottles and autoclaved. Once cooled to 55°C 60µL of 0.8mg/mL bromocresol purple (Sigma) was added and mixed thoroughly. When set, sterile pins and wires were inserted through the agar in the centre of each 200mL Duran bottle and the agar surface seeded with 0.5 McFarland suspension of S *aureus* F2903 using a sterile swab.

Sterilised antimicrobial and control (non-impregnated) collars were applied to the pin using sterile forceps, ensuring that the collar was in contact with the agar surface. The Duran bottles were then sealed and incubated at 37°C. The pin track model was inspected daily for bacteria tracking along the pin/wire and colour change of the agar from purple to yellow which would indicate a change in pH due to glucose fermentation. The collars were transferred to freshly seeded medium each week to avoid accumulation of antimicrobial substances in the agar. Collars were transferred with sterile forceps ensuring that the same side of the disc was in contact with the agar. Tests were carried out in triplicate. This process continued for 16 weeks or until evidence of bacteria extending along the pin track.

To improve visibility and imaging of the experiment, 120mL clear glass French square bottles were used for subsequent method development (Figure 2.4). Ninety eight mL of nutrient agar (75%) with 1mL 0.1% potassium tellurite solution and 1mL 0.1% glucose solution was used for the final test model. Bacterial growth was measured semi-quantitatively, assessing the bacterial growth according to the colour change evident along the wire.

Figure 2.4 Revised pin track model

On completion of the nutrient agar/potassium tellurite experiments, the wires were removed and examined using scanning electron microscopy (S.E.M). Wires were stored in cold acetone to fix the bacteria, and were cut in to 1cm segments and mounted on aluminium stubs using carbon adhesive mounts. Samples were coated with a thin layer of pure gold using Leica EM SCD005 sputter coater and viewed using a JEOL JSM-6060LV variable pressure scanning electron microscope. Microscopy was conducted by an experienced SEM technician who was not blinded to the nature of the experiment or to the origin of the samples.

High Performance Liquid Chromatography (HPLC)

HPLC is used to separate and analyse solutes within a mixture. Solutes are forced at high pressure via the mobile phase solution through a column (stationary phase) which is packed with small diameter porous particles, usually silica. This leads to the separation of the components which can be quantified by the detector at the end of the column. HPLC was used to determine the drug content of the antimicrobial collars and calculate the concentrations released during in-vitro experiments.

Antimicrobial discs were placed in 10mL of chloroform and left for one hour to allow extraction of the drugs. Collars were then removed and placed in fresh chloroform. This process was repeated three times. The chloroform was then evaporated and the drug residue was stored in a freezer until required for HPLC analysis. The drug residue was then reconstituted with 10mL HPLC grade ethanol.

HPLC analysis was performed using an Agilent 1100 HPLC machine (Agilent Technologies, UK) using an Eclipse XDB-C8 (5µm, i.d. 4.6 mm x 150 mm) column (Agilent Technologies). Mobile phases consisted of HPLC grade methanol, and a mixture of sodium dihydrogen phosphate (15mM, pH 2.5) (Sigma) with 10% acetonitrile (Fisher Scientific, Loughborough, UK) which were filtered using a 0.45 µm nylon membrane filter. Injection volume was set at 5µL and flow rate at 1mL/minute. UV detection was set at 254nm. A calibration curve was performed using standards prepared from the three antimicrobials. All tests were carried out in triplicate.

Testing serial impregnation collars

To evaluate the drug content and antimicrobial activity of the collars made using serial impregnation methods, the first and subsequent four batches of antimicrobial collars were tested using HPLC methods previously described. Three collars from each batch were tested using HPLC analysis.

SPTT was conducted to identify differences in duration of antimicrobial activity between the first and fifth batch of collars using *S aureus* F2903. Batch one and Batch five collars were tested in triplicate. Serial impregnations of individual antimicrobials were not tested, as the combined antimicrobials are the focus of the feasibility study. Statistical differences in zone sizes between Batch 1 and Batch 5 were calculated using a two-sample t-test for independent populations using a significance level of 0.05.

2.7 Feasibility study

Patient and public involvement

The intended purposes of PPI in this study were to

- Ensure that the methods proposed were acceptable and compatible with the needs of potential research participants.
- Ensure that the language and content of patient materials were appropriate and easy to understand.
- Establish the concept, acceptability and usability of the antimicrobial collar.

Planned approaches for PPI included

1) Focus groups to discuss the study and patient materials.
2) Unstructured interviews to identify acceptability and usability of the novel design concept.
3) Structured interviews of service users to assess acceptability and usability of the collar.
4) Short questionnaire on preferred collar thickness.

Study design

The PPI facilitator in the local NHS Trust was contacted for assistance. Members of the Nottingham University Hospitals (NUH) PPI database were invited to participate in a focus group, to discuss the nature of the research and patient materials, such as the information sheet and questionnaires. The NUH communications team and the Collaboration for Leadership in Applied Health Research Care (CLARCH) were also contacted by the PPI facilitator as an additional route for PPI.

Focus groups were chosen due to the potential to identify knowledge from the interchange and discussion between participants, which may in turn generate further questions. The advantage of focus groups over a one-to-one interview is the opportunity for participants to reflect and respond to other comments. These spontaneous comments and reflections can lead to a deeper understanding of what is being investigated (Parahoo 2006). Limitations of focus groups include the lack of reproducibility due to many factors, including participant behaviour (Parahoo 2006).

Collar design

Acceptability and usability of collar design

Staff, patients (without external fixators) members of the public, and final year nursing students working in orthopaedics were approached for opinions on the use of the collars. Student nurses were included as they hold clinical knowledge regarding desirable/undesirable properties of dressings, yet are impartial to the local cultures and politics which may influence the permanent staff.

Staff were approached individually to prevent influence from others which may bias the opinion given. All were asked to handle the collars and discuss what they thought about the concept and identify any aspects of the collar which they thought would be challenging or problematic. Feedback was divided into common themes in the categories: positive comments, potential problems/ concerns, suggestions and general comments.

The use of qualitative, non-directive interviews gives respondents the opportunity to frame answers in their own words (Parahoo 2006). As the collar is a new concept in preventing PSI a qualitative approach was required to understand the thoughts, concerns and expectations of the novel device. Through interviewing multiple participants, multiple realities can be explored (Cresswell 2009), both from patient and health care workers' perspective. This approach can identify many factors surrounding the antimicrobial collar and establish comprehensive opinion from different viewpoints; however it is not measurable using conventional scales.

Service user evaluation of prototype collars

Prototype (non-antimicrobial) collars were sterilised and available for patients with external fixators to apply around pin sites to assess sizing, ease of use and comfort. Feedback on initial thoughts of the collars were sought to establish acceptability and usability of the product. Waltz et al (1991) advocates the structured interview as the most appropriate tool when identical information is needed from all respondents. As the questions or participant responses may require clarification an interpersonal approach was selected over a written questionnaire. A structured interview with predetermined questions was designed by the researcher. The interview schedule (Appendix 4) was tested for face validity with clinical, academic colleagues and members of the general public and one question was removed due to ambiguity before administering the questionnaire in the clinical setting. The interview was administered to all respondents in the same manner.

Patients with external fixators were asked about initial thoughts on the prototype collars. Patients were asked to reply yes, no or don't know to the direct questions. Free comments were sought at the end of the questionnaire.

Collar thickness

Current service users, nursing, medical and physiotherapy staff, directly involved with either using or caring for external fixators were surveyed regarding preferred thickness of the prototype collars. Each person was shown three thicknesses (1mm, 2mm, 3mm) and asked to select which thickness they thought would be ideal for use. Comments were sought on potential reasons for the choices made.

Development of study protocol

In order to determine the effectiveness of the antimicrobial collar in a clinical population systematic and purposeful measurement of concepts and variables is required (Parahoo 2006). Controlled trials are an effective method of assessing causality (Torgeson and Torgeson 2008) through quantitative measures to determine whether interventions have the desired effects (Parahoo 2006). This study used a single-centre, parallel, randomised control feasibility study to assess the acceptability of the antimicrobial collars and the study feasibility.

Control and comparison groups

While it is common for studies to include more than one comparative group, it is important to consider the merit of each type and the benefit to the trial. The European Medicines Agency (2001) describes control treatment as either the use of a placebo, no treatment, use of a different dose or regimen or use of a different active treatment.

The traditional view of RCT's is a double blinded approach to randomisation to compare active and placebo products (Torgerson and Torgerson 2008). However, the use of a placebo collar (non-antimicrobial) was decided against for the following reasons:

- A placebo collar may cause local skin irritation, skin maceration and/or fungal infections underneath the collar.

- A placebo collar may act as an additional surface for bacteria to colonise, and therefore act as an additional source of infection and increase the risk of PSI.

- Patients and clinicians would not be adequately blinded to group allocation due to the orange colour of the antimicrobial collars.

A search for other potential study comparators was conducted and GuardIVa was identified as a potential product, marketed as an antimicrobial haemostatic dressing. While the product showed promise with regard to haemostatic properties and chlorhexidine antimicrobial action this product was not included in the feasibility study as it required securing with other products. Recommended securing dressings included transparent waterproof dressings such as Opsite or Tegaderm, which were considered difficult for patients to apply and remove. This may increase reliance on family/health care services to carry out dressing changes, and potentially result in non-compliance with pin site care. Film dressings can be uncomfortable to remove and may lead to non-compliance with pin site care and consequently affect patient outcome and clinical effectiveness as a treatment. Failure to redress pin sites where fluid has accumulated may result in fluid being maintained at the pin site and subsequently increase

the risk of infection (Clasper 2001b). The use of these securing dressings would have also affected other variables, such as creating a different wound environment which alters the humidity and temperature of the wound. The use of a semi-permeable dressing such as Opsite may also reduce the ingress of bacteria, and would therefore not offer a true comparison in a clinical trial against the antimicrobial collar.

As current commercial products and placebo collar were not considered to be suitable treatment arms for the study, the intervention group (antimicrobial collar) was compared with standard care (no collar). While this does not conform to the traditional 'gold standard' double-blind placebo controlled design, the 'open trial' design facilitates greater involvement with participants regarding collar design and future product development.

Participants and study setting

Potential participants were identified by the orthopaedic team. Prospective participants who were eligible for inclusion in the study (Table 2.3) were provided with verbal and written information concerning the purpose of the study (Appendix 5) before informed consent was obtained (Appendix 6).

Table 2.3 Inclusion and exclusion criteria

Inclusion criteria
Has either fracture or pathology requiring the use external fixation, limb reconstruction using external fixation or cervical spine pathology requiring halo immobilisation.
Over 18 years of age and has the mental capacity to provide informed consent.
Able to read the patient literature and understand verbal information regarding the study.
Exclusion criteria
Known allergy to the antimicrobials used within the devices.
Previous medical history of osteomyelitis at the site of pin placement.
Pregnancy – women who were pregnant or expected to become pregnant during the study period.
Patients taking long-term antibiotics.
Participation in other clinical trials involving a medicinal product (CTIMP) drug or device within the last 6 months.
Current osteomyelitis or systemic infection.

A pragmatic sample size of 50 participants was set based on expected numbers of patients treated with external fixator devices during the study period. It was projected that 50 participants would be an achievable number for the feasibility study and would be sufficient to assess the practicability of trial numbers for a further efficacy study. Using data from James et al's (2014) retrospective analysis of 1592 consecutive cases in which infection rate was reduced from 8.4% in non-antimicrobial shunts to 5% with antimicrobial-impregnated shunts, a total sample size of 1692 participants would be required to have an 80% chance of detecting significance at 5%, as calculated using Sealed Envelope power calculator for binary outcomes (2012).

The feasibility study was conducted at Nottingham University Hospitals NHS Trust, which was established as a major trauma centre in 2012. Participants were recruited on the orthopaedic trauma wards or major trauma unit. Follow-up was conducted in the orthopaedic out-patient department.

Randomisation

Blocked randomisation was used to allocate participants to standard care or active intervention study groups to reduce the possibility of chance imbalances (Torgerson and Torgerson 2008, Akobeng 2005, Pocock 1983), and remove potential bias in the allocation of subjects to control or intervention groups (Parahoo 2006). Randomisation was stratified according to location of external fixator (halo or lower limb) to ensure equal distribution of frame types between study groups.

Group allocation was determined using a web-based program set up by the clinical trials unit. Patients were enrolled by the researcher obtaining consent. Due to the nature of the study it was not possible to blind the participants or the researcher to the group allocation.

Study groups were followed up identically throughout the study period. All participants were under the care of orthopaedic consultants at the Nottingham University Hospitals NHS Trust, and frequency of follow-up visits was determined by the clinical team, rather than by research protocol.

Research and ethical approval

Sponsorship for the feasibility study was obtained through the University of Nottingham (Appendix 7) and approval obtained from Nottingham University Hospitals Research and Innovation department (Appendix 8). The MHRA advised that further approval was not required for a local trial of the antimicrobial collar.

Ethical approval was granted from Nottingham Research Ethics Committee (Appendix 9) and the protocol underwent a major amendment (23/9/2013) to increase recruitment rates. The major amendment covered inclusion of all external fixator devices and recruitment period was extended from 72 hours after frame application to 96 hours.

Pin site care

As the cleansing protocol used for the feasibility study does not consistently align with the current UK 2011 national consensus guidelines (Timms et al 2011) each point is discussed in relation to current evidence.

Cleansing

UK national consensus guidelines (Timms et al 2011) recommend cleansing with alcoholic chlorhexidine due to its long-acting antimicrobial activity. The MHRA (2012a, 2012b) notes that chlorhexidine is a known risk for hypersensitivity, generalised allergic reactions and anaphylaxis, although the prevalence of chlorhexidine hypersensitivity remains unknown. The study protocol cleansed pin sites with 0.05% alcoholic chlorhexidine solution and observed for signs of hypersensitivity/allergic reactions. Insufficient evidence is available to guide frequency of pin site care so as to prevent PSI. Therefore the national consensus recommendation of cleansing at least once weekly and more frequently with suspected infection or increased secretions, was accepted as the study protocol. Only crusts extending up the pin were removed during routine pin site care, in accordance with the consensus document.

Timing of post-operative dressing

A lack of national consensus regarding the timing of the first post-operative dressing change was reported by Timms et al (2011). Owing to a deficit in rigorous studies concerning the timing of initial dressing changes this aspect of care remained the remit of the clinical team. Surgical dressings were changed on the ward prior to patient discharge to allow assessment of pin sites by the clinical team and to enable patient instruction on pin site care.

Pin site dressings

Pin sites were dressed at the discretion of the clinical team. Pins could remain uncovered if well healed and not leaking exudate and patients preferred not to use dressings. The exception was participants in the intervention group where pin sites were covered using the experimental collar. In keeping with Timms et al (2011) recommendations, pin sites requiring dressings were re-dressed every seven days unless there was copious discharge, in which case dressings were changed when required. The intervention group had collars removed at least every seven days, washed and re-applied until collars required replacing at 3 months.

The role of compression in pin site care

Timms et al (2011) suggested that compression applied at the pin sites reduces movement at the skin/pin interface and helps to prevent haematoma formation and "tenting of the skin by helping the wire to 'cheese wire' through the soft tissues". No evidence is available to demonstrate the effectiveness of compression in preventing haematomas or infection, or to substantiate proposed benefits, required level of compression or complications that may occur as a result of continued pressure over prolonged periods. Compression of pin sites was therefore not applied in this study.

Showering/bathing with an external fixator in-situ

The use of showering has been discussed by Gordon (2000), and Sims and Saleh (2000), though in the absence of a controlled trial, clear conclusions cannot be drawn. Timms el al (2011) recommended showering either immediately prior to dressing changes, or that the fixator should be kept dry during showering. These recommendations were accepted for the feasibility study.

Summary of cleansing protocol

In summary pin site care comprised of the following regime:

- Pin sites were cleansed at least once weekly with alcoholic chlorhexidine.
- Scabs and adherent crusts were not actively removed during routine care, although dried exudate on pins were removed.
- Pin sites were dressed in the presence of exudate and at the discretion of the clinical team. Patients in the intervention group had impregnated collars around the pin sites which were removed for cleansing every seven days and replaced every 3 months.
- Patients were permitted to shower, although it was recommended that the fixator should be kept dry or pin sites cleaned immediately afterwards.
- Compression was not applied to pin sites.

The study protocol is included in Appendix (10).

Assessment tools and data collection

Participants were assessed by the researcher at each clinic appointment using the case report form (CRF) (Appendix 11). Primary outcome measures were the number of patients with PSI and number of infected pin sites. Secondary outcome measures included adverse reactions to the collars, health care utilisation (antibiotic use, admission to hospital and removal of external fixation due to infection) and severity of infection. Pin sites were evaluated using predetermined assessment criteria and were swabbed for clinical and research purposes if infection was suspected, as approved by the local research ethics committee (Appendix 10 and 11). General feedback was collected on the use of the antimicrobial collars (intervention group) and any problems experienced with the pin sites.

Analysis

Employment was categorised using the International Standard Classification of Occupations (ISCO-08, International Labour organisation 2007). Analysis was based on intention-to-treat (ITT) as it reflects deviation from protocol which may occur in routine clinical practice and assumes equal risk of non-compliance with the study protocol in each group (Wang and Bakhai 2006).

Data analysis was completed using SPSS. Group characteristics were compared using Pearson chi-squared test for categorical variables, and Student t-test for continuous variables. Severity of infection was analysed using one-way ANOVA. Survival time till infection was compared using Kaplan-Meier survival analysis to allow for different lengths of follow-up.

Patient evaluations

While it is important to evaluate the safety and clinical outcomes of the study, it is also important to assess the effectiveness of the care from a patient perspective.

Evaluation of collars

Subjective feedback and open comments regarding the use of the collars were documented at each follow-up. Participants in the intervention group were sent questionnaires by post (Appendix 12) within two weeks of frame removal enquiring about their experience of using the collars and comments on the product design. A second request was sent two months following removal of the frame if a reply had not been received.

Patient-reported outcome measures

Patients with external fixator devices were asked to specify up to two desired outcomes following completion of treatment. Responses were sought before patients were discharged from hospital following application of the frame. Free text answers were recorded so that participants were able to answer freely and not constrained to predetermined outcomes of the research or clinical team.

Patient-reported experience measures

Patients with external fixators were asked during outpatient appointments what factors they considered to be important aspects of their care, which features could be measured as part of future experience evaluation tools, and what aspects they felt affected their experience and satisfaction with the service. Open ended questions were used to allow participants to frame answers in their own words. Free text answers were recorded to facilitate answers which were not constrained to predetermined outcomes of the research or clinical team.

Chapter 3 Results

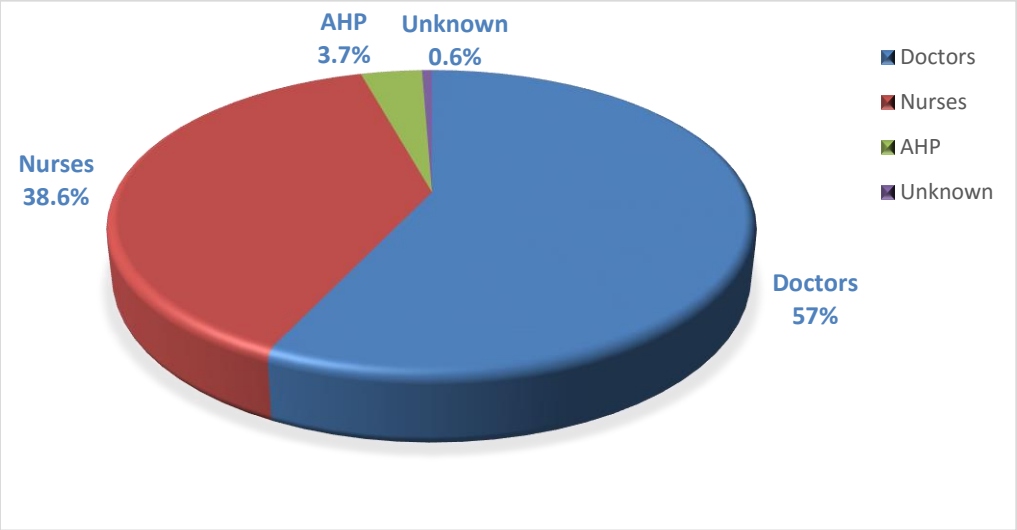
3.1 Survey of current pin care regimes

Three hundred and sixty-nine people completed the questionnaire, although 48 were excluded due to substantial missing data. The data were analysed from the remaining 321 responses giving a final response rate of 23.7%. The response rate from UK practitioners was 37.3%.

Demographics

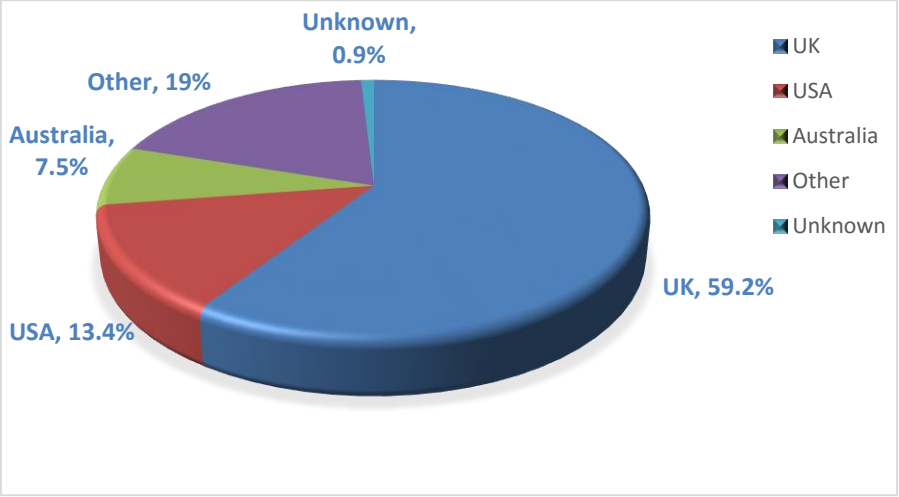
Three hundred and nineteen respondents identified their role. The sample consisted of 57.0% (n=183) doctors, 38.6% (n=124) nurses and 3.7% (n=12) allied health professionals (AHP) which included orthopaedic practitioners (n=4), orthopaedic technicians (n=2), researchers (n=2), auxiliary nurse (n=1), occupational therapist (n=1), physician's assistant (n=1), physiotherapist (n=1). Profession was not stated in two cases (0.6%). This is summarized in Figure 3.1.

Figure 3.1 Professional groups



The majority of respondents were from the United Kingdom 59.2% (n=190), USA 13.4% (n=43) and Australia 7.5% (n=24). Three respondents did not specify location of practice (0.9%). The remaining 19.0% of respondents (n= 61) were from New Zealand (n=8), Canada (n=6), Sweden (n=5), Egypt (n=4), India (n=4), Germany (n=4), Holland (n=3), Italy (n=3), Netherlands (n=3), Greece (n=2), Israel (n=2), Japan (n=2), Singapore (n=2), Switzerland (n=2), Armenia (n=1), Brazil (n=1), Denmark (n=1), Malta (n=1), Malawi (n=1), Mexico (n=1), Nepal (n=1), Puerto Rico (n=1), Slovenia (n=1), South Africa (n=1) and Turkey (n=1). This is summarised in figure 3.2.

Figure 3.2 Country of response



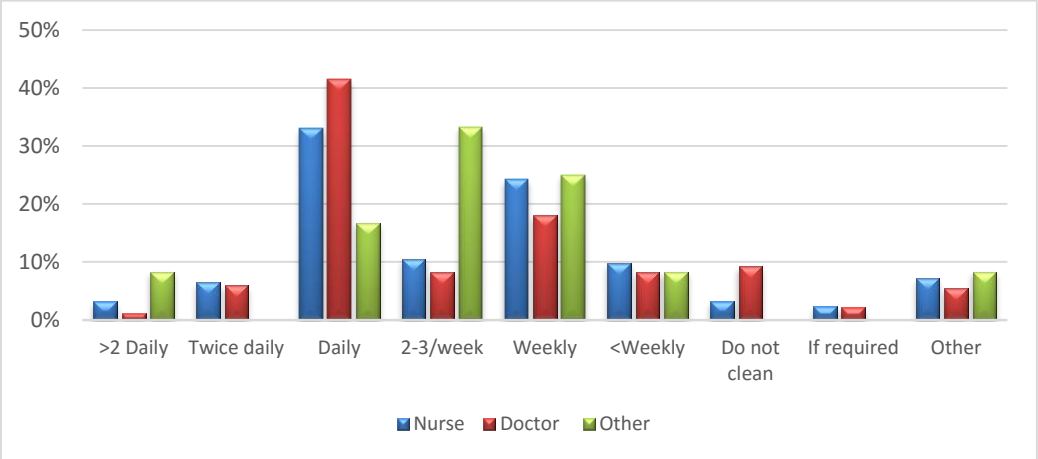
Of those who responded from the UK, 75 were nurses, (36 nurses, 25 nurse specialists, 11 nurse practitioners and 3 other roles), 106 doctors (13 doctors and 93 consultants), 4 orthopaedic practitioners, 1 orthopaedic technician, 1 physiotherapist and 1 auxiliary nurse. Two UK respondents did not specify their clinical role.

Frequency of care

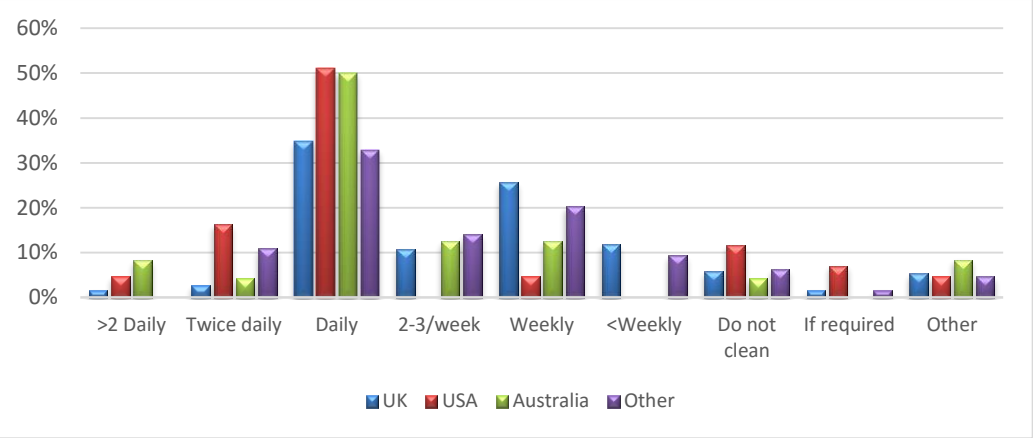
Respondents were asked how frequently pin sites should be cleansed. A clear response was not identified by 4.7% (n=15). Twenty-one (6.5%) reported that they did not clean pin sites. The single largest group of respondents (37.4%, n=120) cleansed pin sites daily. Pin sites were cleansed 2-3 times weekly by 10.0% (n=32), weekly by 20.6% (n=66), and less frequently than every seven days by 8.7% (n=28). Other frequencies of cleansing include more than twice daily, twice daily and if required 2.2% (n=7), 6.2% (n=20), and 2.2% (n=7) respectively. Pin sites were not cleansed by 0.6% (n=2) if pin sites were dry. Frequency was determined by consultants in 0.9% (n=3). Responses categorised by country and profession are summarised in Figure 3.3. Frequency of care varied significantly between professions (p=0.02), and between country (p=0.0001).

Figure 3.3 Frequency of care

a) Frequency of care by Profession



b) Frequency of care by country



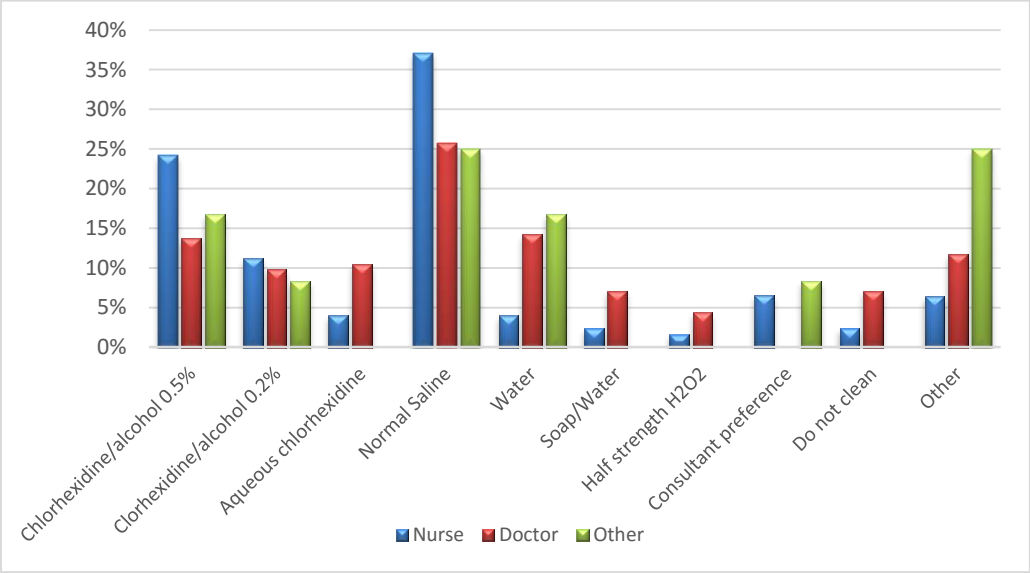
Cleansing pin sites

Alcoholic chlorhexidine and normal saline were the preferred cleansing agents of the majority, with 30% (n=96) using normal saline and 29.6% (n=95) using alcoholic chlorhexidine. Other common solutions included water (10.6% n=34), aqueous chlorhexidine (7.5% n=24), soap/shampoo and water (5% n=16) and half strength hydrogen peroxide (3.1% n=10).

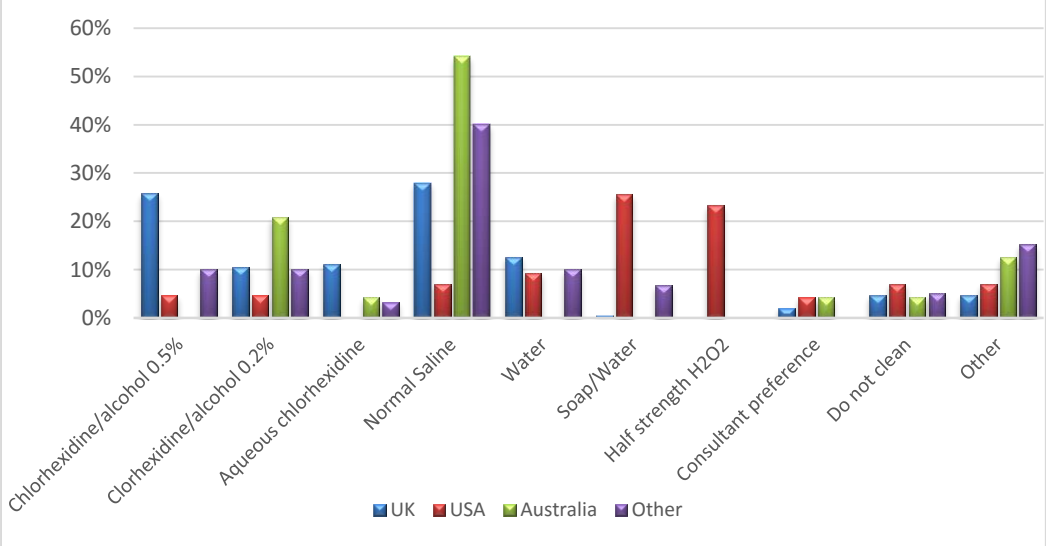
Less common cleansing agents included povidone iodine (3.1% n=10), although it was not specified if this was aqueous or alcoholic, alcohol wipes (0.6% n=2), povidone iodine and hydrogen peroxide (0.3% n=1), inadine (0.3% n=1), prontosan (polyhexanide and betaine) (0.3% n=1), Levomekol (chloramphenicol and methyluracil) ointment (0.3% n=1), warm salty water (0.3% n=1), 70% alcohol solution (0.3% n=1), and standard disinfection agent and soap (0.3% n=1) although the disinfection agent was not specified. Sixteen respondents (5%) reported that they did not clean pin sites. Significant differences were identified between professions ($p= 0.000025$) and country ($p<0.001$) (Figures 3.4).

Figure 3.4 Cleansing agents

a) Cleansing agents by profession



b) Cleansing agents by country

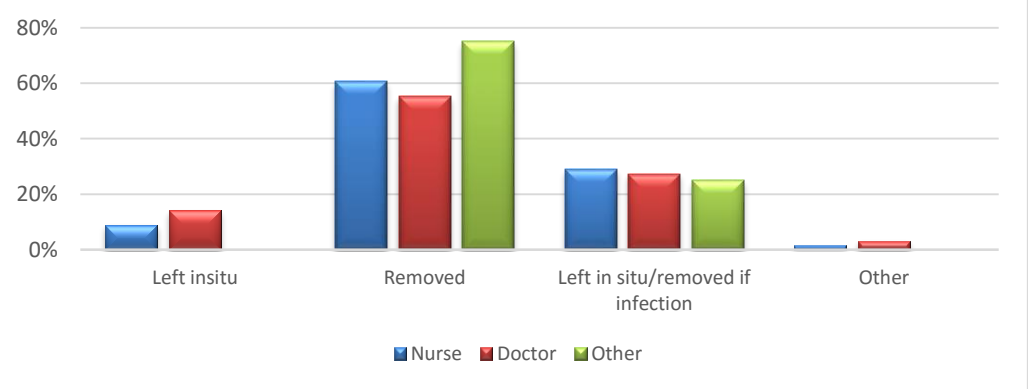


Crusts

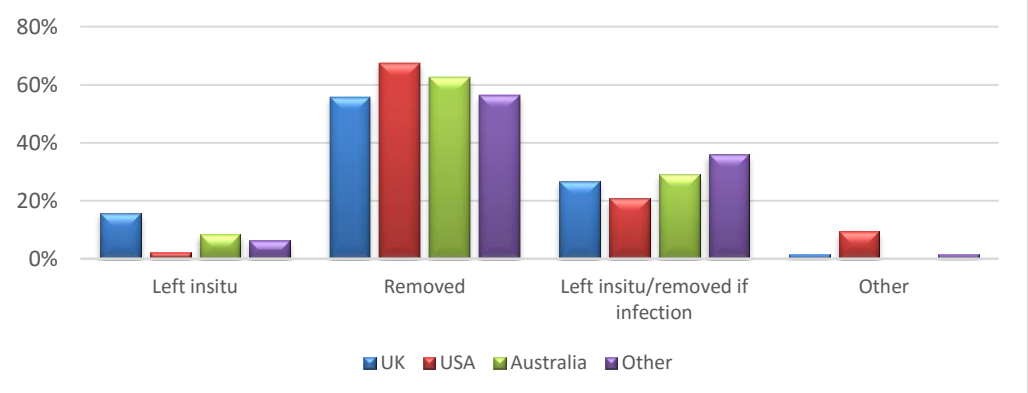
Crusts and dried exudate were left in-situ by 11.5% (n=37), 28% (n=90) left crusts/dried exudate in-situ, although removed if infection was present, and 57.9% (n=186) removed crusts and dried exudate. An unclear response was given by five respondents (1.6%), and practices varied depending on consultant preference as reported by three (0.9%). No significant differences were identified between country (p=0.08) or profession (p=0.34) (Figures 3.5).

Figure 3.5 Crust management

a) Crust management by profession



b) Crust management by country

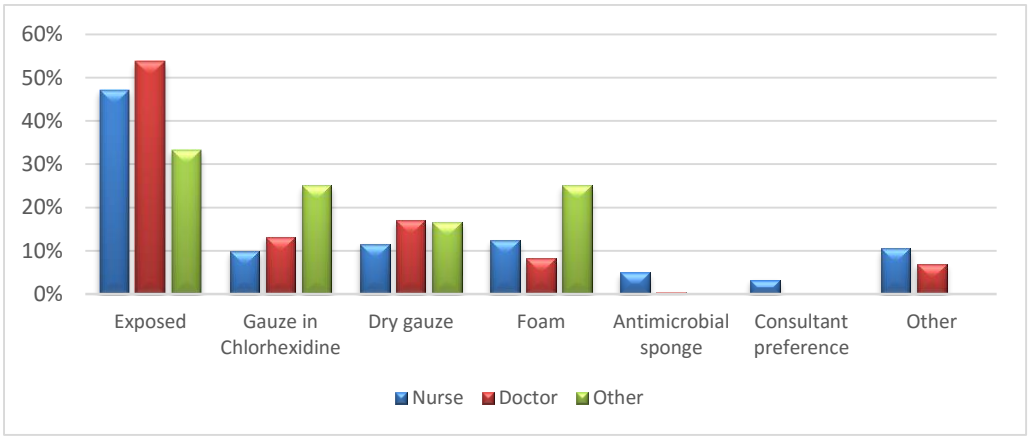


Dressings

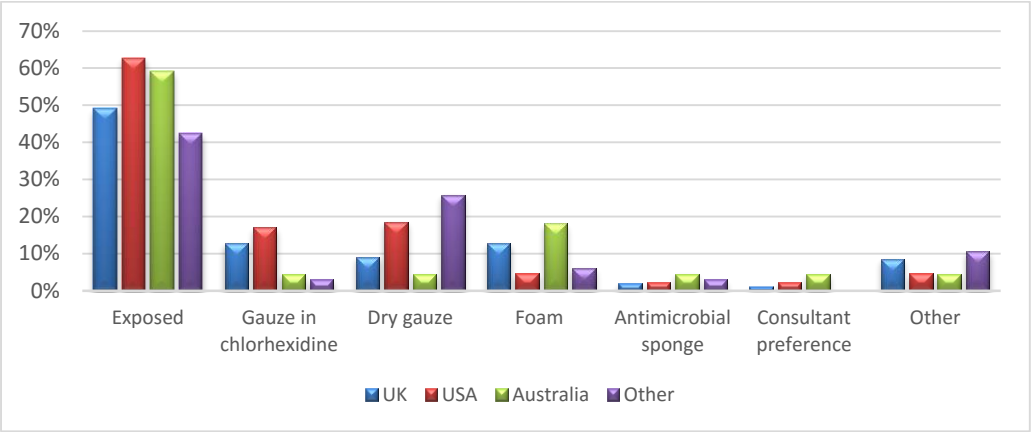
Pin sites were left exposed by 50.3% (n=160), whereas 13.5% (n=43) used dry gauze to dress pins, 12.9% (n=41) used gauze soaked in chlorhexidine and 10.7% (n=34) preferred foam dressings. Other choices of dressings included sponge, soaked/antimicrobial sponge, non-adherent dressings and a combination of dressing and bandage were reported at 1.3% (n=4), 2.5% (n=8), 1.3% (n=4), 1.9% (n=6) respectively. Other dressings were reported by 8.2% (n=26) and included figure of eight bandaging, inadine, silver, Vaseline gauze, Urgatul, Sponguse simple, Fitostimoline, cling wrap, Allevyn soaked in chlorhexidine, jellonet, Activion (manuka honey) and Bactroban ointment. Dressing choice was determined by consultants in 1.3% (n=4). Responses categorised by country and profession are summarised in Figure 3.6. No significant differences were identified between professions (p= 0.39) or country (p= 0.11) as to whether pin sites are covered or left exposed.

Figure 3.6 Pin site dressings

a) Pin site dressings by profession



b) Pin site dressings by country

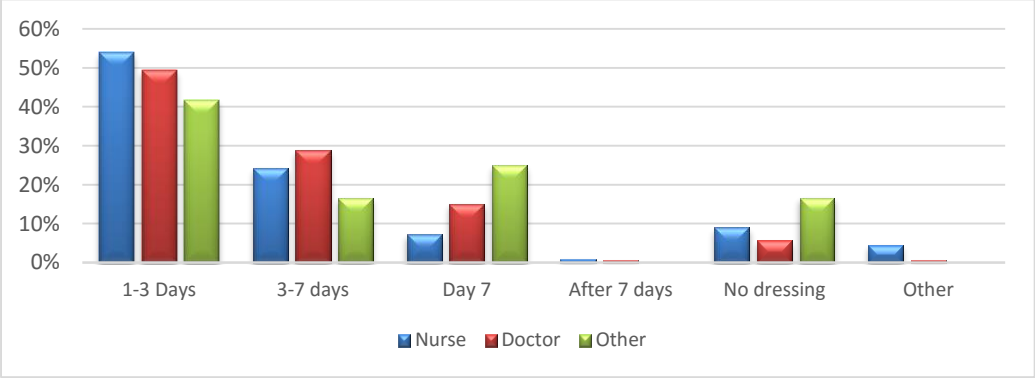


Surgical dressing change

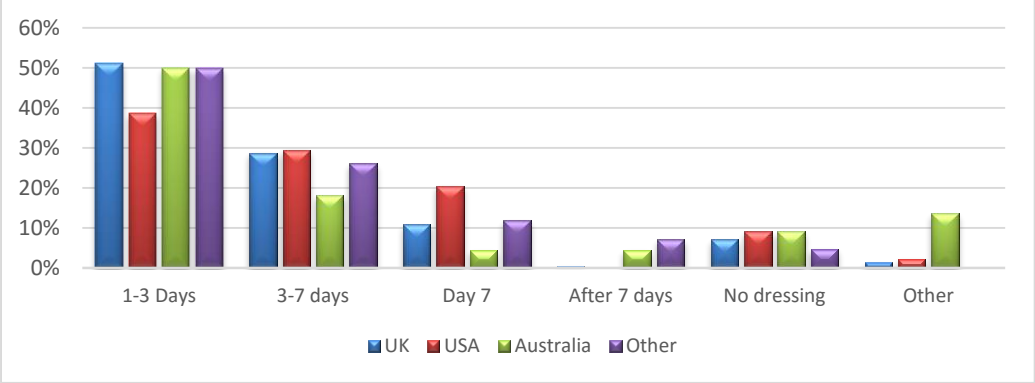
Initial surgical dressings were removed by 50.8% (n=153) between 1-3 days following surgery, 26.6% (n=80) between 3-7 days, 12.6% (n=38) at 7 days and 7.3% (n=22) state that no surgical dressings were used. Other responses included surgeon preference (0.7%, n=2), when clinically indicated or when pins were dry (1.0%, n=3). One practitioner highlighted that there were no set guidelines for this aspect of care (0.3%, n=1). Significant differences were identified between country (p=0.005) although not between professions (p=0.05) (Figure 3.7).

Figure 3.7 Surgical dressing change

a) Surgical dressing change by profession



b) Surgical dressing change by country

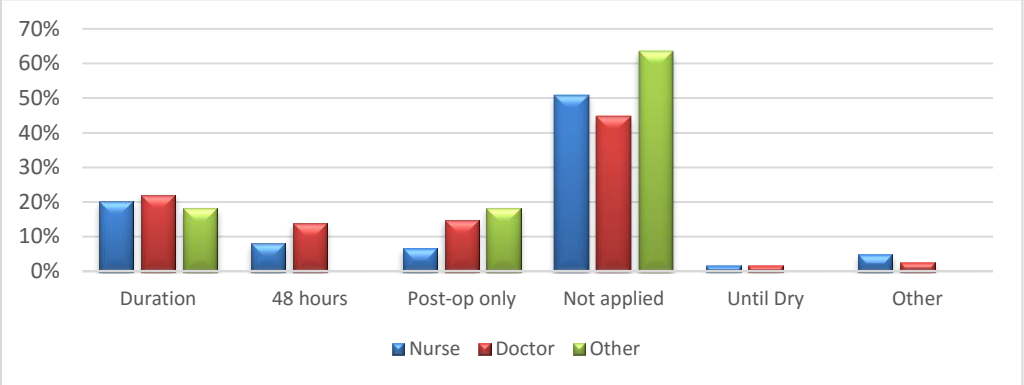


Compression of pin sites

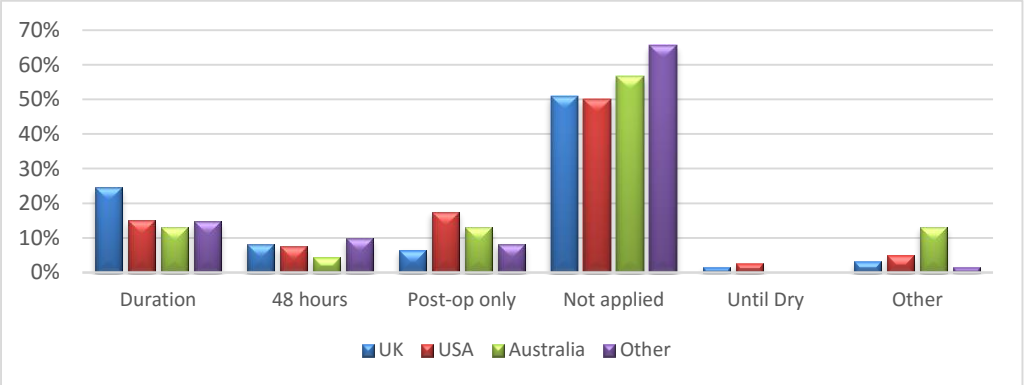
Compression of pin sites varied with 20.5% (n=64) applying compression for the duration of external fixation, 11.9% (n=37) in the immediate post-operative period, 11.2% (n=35) for the first 48 hours, and 1.6% (n=5) until the pin sites were dry. Other responses included consultant preference (0.3%, n=1), 2-7 days (0.9%, n=3), 1-3 weeks (1.3%, n=4), and dependent on the site where the pin is placed (0.6%, n=2). Compression was not applied to pin sites by 51.6% of respondents. No significant differences were observed between country (p=0.07) although were apparent between professions (p=0.009) (Figure 3.8).

Figure 3.8 Use of compression

a) Use of compression by profession



b) Use of compression by country



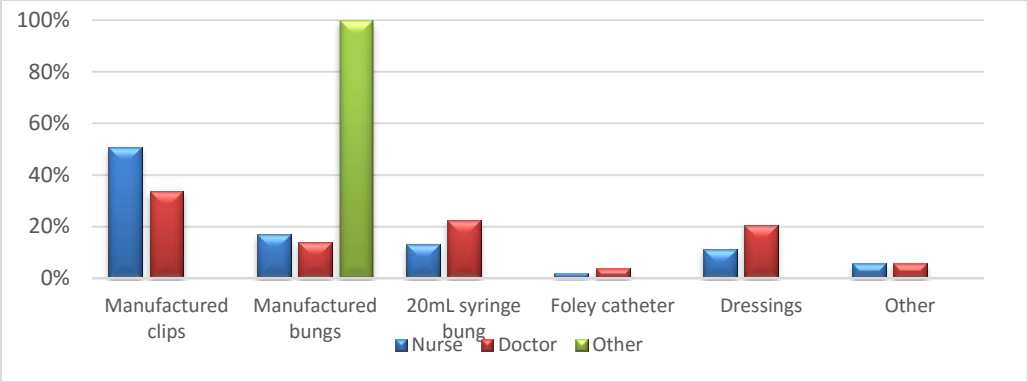
Devices used to apply pin site compression

One hundred and sixty two respondents (50.6%) provided information on the devices used to apply compression at pin sites. Manufactured clips were the most common device used, followed by tightly applied dressings and bungs made from 20mL syringes which were used by 38.9% (n=63), 17.3% (n=28) and 19.1% (n=31) respectively. Other common devices included manufactured bungs (16.1%, n=26) and bungs made from Foley catheters (3.1%, n=5). Other responses accounted for 5.6% (n=9) which included spindle tools, umbilical clips, rubber button discs, bungs from antibiotic vials, tap washers, suction tubing and washers made from car

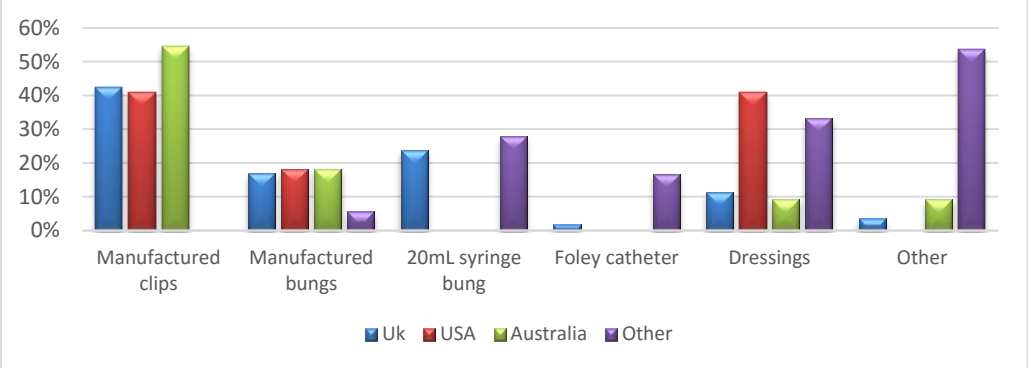
tyres. One respondent from the UK specified that manufactured clips were used initially, but if these become lost or broken, hair grips were used as a replacement. Results according to profession and country are summarised in Figure 3.9.

Figure 3.9 Compression devices

a) Compression devices by profession



b) Compression devices by country



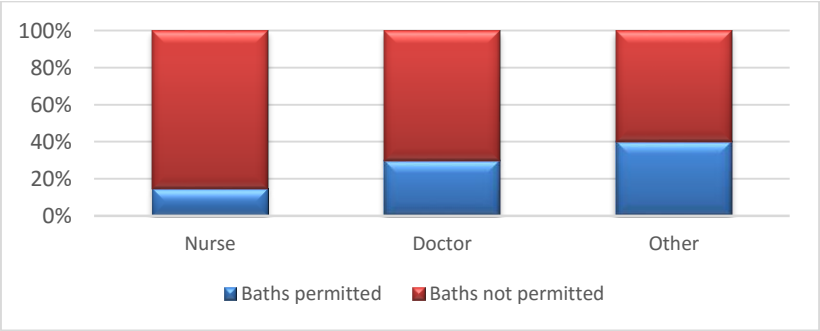
Bathing and showering

Only 26.8% (n=80) permitted bathing whilst in an external fixator, and 82.0% (n=242) permitted showering. Additional free text responses revealed that a small number of practitioners permitted patients to swim in chlorinated pools (3.0% n=9), or swim in the ocean (1.3%, n=4). The majority of those who specified that swimming in the ocean or sea were permitted were from the USA (58%, n=7), and were medically qualified practitioners (84.6%, n=13). No statistical differences were identified

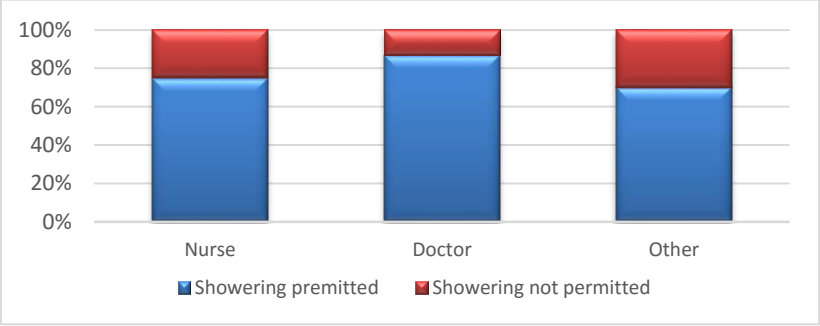
between country regarding decisions to bath (p=0.16) or shower (p=0.19), although statistical differences were identified between professions for bathing (p=0.004) and (p=0.009) for showering (Figure 3.10).

Figure 3.10 Bathing and showering practices

a) Bathing practices



b) Showering practices



UK practice and national consensus guidelines

Of those who responded from the UK, 47.9% (n=34) UK nurses (C.I. 0.363-0.595) and 38.2% (n=71) UK clinicians (C.I. 0.311-0.453) cleansed pin sites with alcoholic chlorhexidine as recommended by Timms et al (2011). The majority of UK nurses reported covering pin sites in accordance with RCN guidelines (56.9% n=41) (C.I. 0.455–0.683) as with 50.3% (n=93) UK clinicians (C.I. 0.431-0.572). Although only 26.3% (n=20) UK nurses (C.I. 0.184-0.306) and 24.5% (n=46) UK clinicians (C.I. 0.163–0.363) reported the use of compression as suggested by RCN

consensus guidelines. Responses identified 78% (n=51) UK nurses (C.I 0.685-0.885) and 85.6% (n=174) UK clinicians (C.I. 0.804-0.908) allow patients to shower and bathing was not permitted by 84.6% (n=55) by UK nurses (0.759-0.934) and 71.3% (n=137) UK clinicians (C.I. 0.708-0.732) as advised by current consensus guidelines.

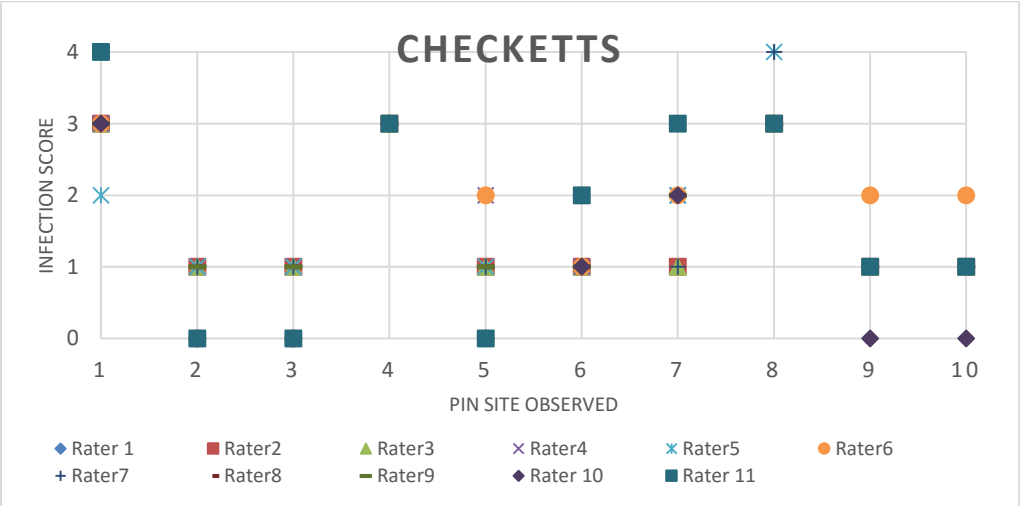
3.2 Assessment tools

Assessors unanimously agreed the rating of infection for one pin site for each tool. Interestingly this was pin site four using the Checketts score and pin site three using the Patterson and Santy tools. Using the individual classification criteria, assessors agreed on a diagnosis of mild (score ≤3) or severe (score ≥4) infection ratings for 80% of pin sites using the Checketts tool. An agreed diagnosis of 'moderate' (score >3) or 'severe' (score >7) infection was not achieved for any of the pin sites using the Patterson tool. Equally, the four pins which were considered to have mild infection using the Patterson score, were also considered by some assessors as having a score of zero, representing 'no infection'. The Santy tool does not offer numerical criteria for the grade of infection and therefore was not analysed in this manner. Raw data from assessors are summarised in Figure 3.11. Single measures intraclass correlation coefficient was reported at 0.814 for Checketts (Cronbach's Alpha 0.981), 0.621 for Patterson (Cronbach's Alpha 0.95) and 0.866 for Santy (Cronbach's Alpha 0.989).

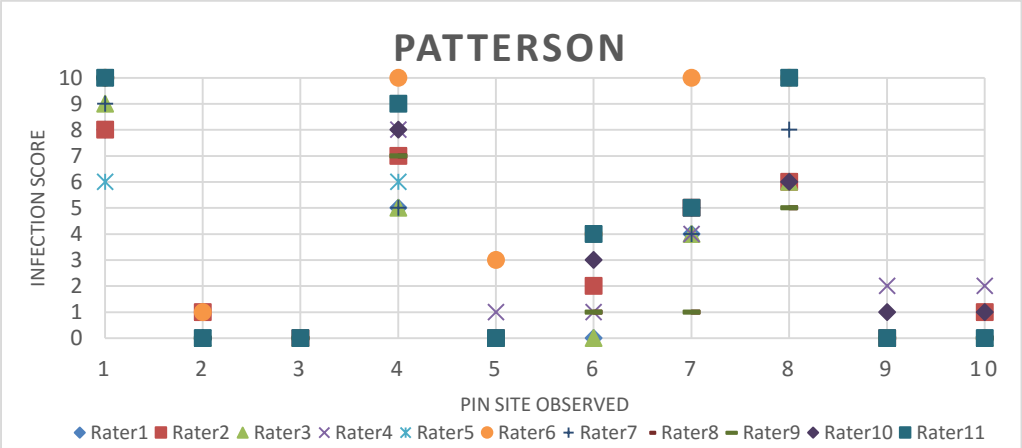
Results were excluded from two assessors due to incomplete re-test data. Based on six clinicians test-re-test score data significant interaction between the observer and the time were identified for the Checketts tool, $F(5, 45)=5.392$, $p=0.01$. No significant interaction was observed for the Patterson scoring tool $F(5, 45)=1.051$, $p=0.4$ or Santy $F(5, 45)=3.953$, $p=0.05$.

Figure 3.11 Infection scores

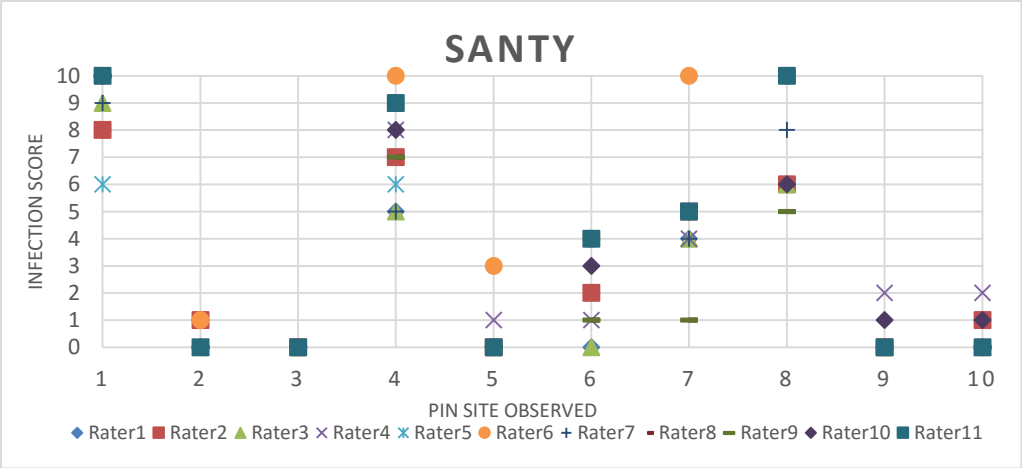
a) Infection scores using Checketts classification



b) Infection scores using Patterson classification



c) Infection scores using Santy classification



3.3 Evaluation of bacteria colonising pin sites

Swabs were obtained from 27 patients (22 male, 5 female). Two hundred and eighteen swabs were processed resulting in 439 bacterial isolates being identified (Figure 3.12). This equated to approximately 2.01 isolates per swab (median 2, range 0-8). The largest group of isolates identified belonged to the Staphylococcus genus (42.8% n=188) with *S epidermidis* accounting for 14.8% (n=65) of the total isolates. Further analysis of staphylococcal group are included in Figure 3.13. Overall, 4.1% (n=18) isolates were identified as *S aureus*, of which 11% (n=2) were methicillin resistant. Corynebacteria accounted for 10.7% (n=47) (Figure 3.14) and other gram positive bacilli (7.5% n=33) included brevibacterium (n=12), cellulomonas (n=10) and rhodococcus (n=4). Gram negative bacilli accounted for only 3% (n=13) and included *Pseudomonas* spp (n=4), *Sphingomonas* spp and *Brevundimonas vesicularis*. The most common anaerobe isolated was *P acnes* (5.5% n=24). Other anaerobes included *Clostridium* spp (2.1% n=9) (*C perfringens* (n=3), *C difficile* (n=2), *C sporogenes* (n=2), *C Sordelli 2*, and *C bifermentans*), *Bacteroides ureolyticus* (n=4), *Gardnerella vaginalis* (n=2) and *Finegoldia magna* (n=2).

Figure 3.12 Bacteria from clinically non-infected pin sites

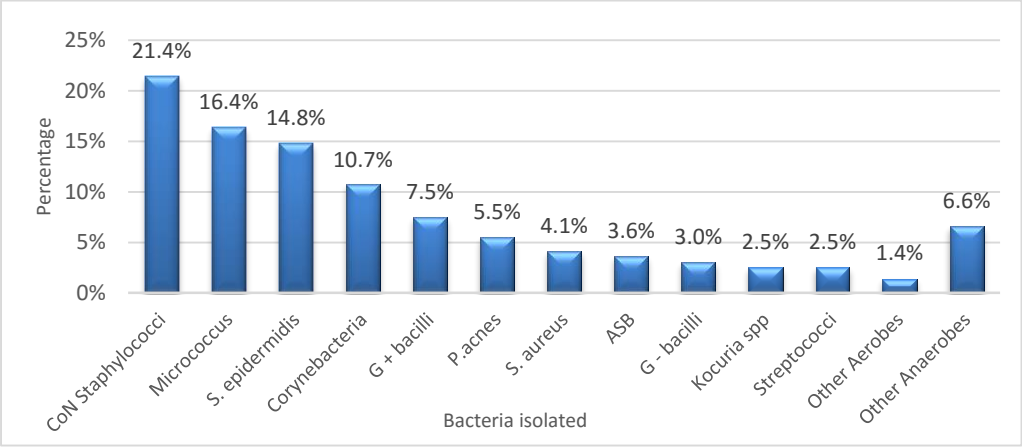


Figure 3.13 Staphylococci identified from clinically non-infected pin sites

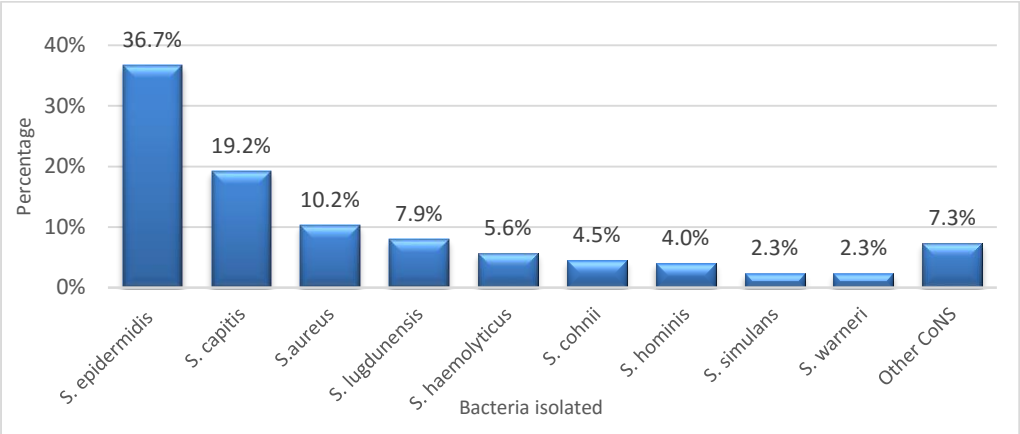
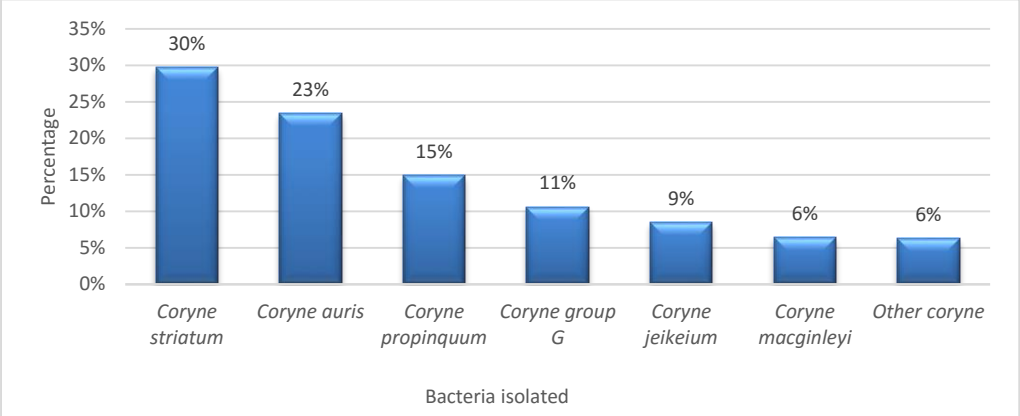


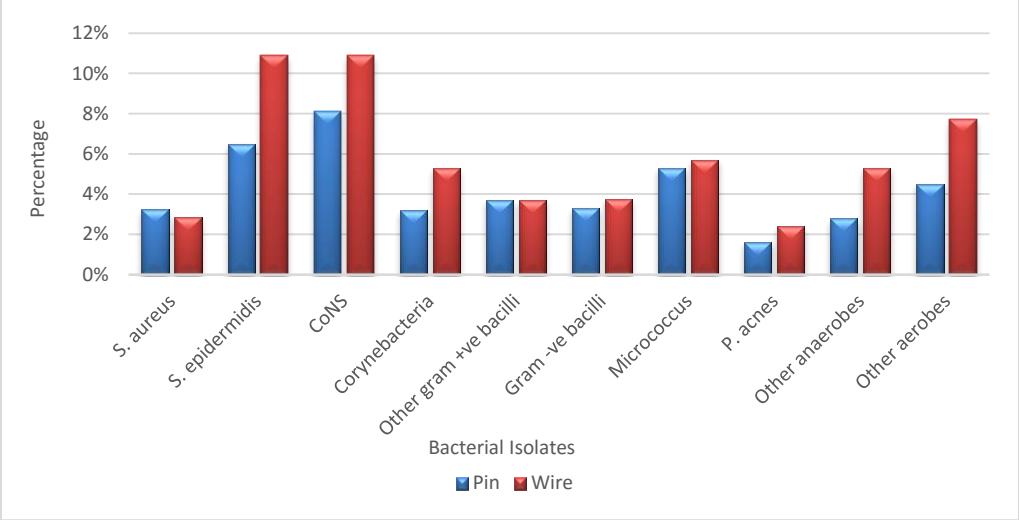
Figure 3.14 Corynebacteria isolated from non-clinically infected pin sites



One hundred and twenty seven swabs from 19 patients were included for further analysis using details of site of insertion and whether this was a pin or wire. There were no statistically significant differences ($p > 0.05$) in the type of bacteria isolated at the different tibial sites. A small increase in the number of isolates identified at proximal tibial sites were observed compared to distal tibial sites, with an average of 2.4 isolates per swab (median 2, range 0-8), (n=45) proximally and 1.98 per swab (median 2, range 0-6) (n=43) distally. Mid tibial sites had an average of 1.89 isolates per swab (median 2, range 0-5) (n=19) and wires to the foot had an average of 0.22 of isolates per swab (median 0, range 0-3) (n=18). Only two femoral pins were swabbed as part of this evaluation, and no bacteria were isolated from these.

Overall, tibial pins had an average of 2.45 isolates per swab (median 2, range 0-8) (n=40), compared to an average of 1.96 for wires (median 2, range 0-8) (n=67). The type of isolates identified were comparable between clinically non-infected pins and wires, with no statistically significant differences identified (p>0.05). A summary of data from tibial pins and wires is presented in Figure 3.15.

Figure 3.15 Bacteria isolated from non-infected tibial pins and wires.



3.4 Evaluation of bacteria from pin site infection

Swabs were obtained from 29 patients (22 male, 7 female). One hundred and twenty four swabs were processed and 256 bacterial isolates were identified (Figure 3.16). This equated to approximately 2.06 isolate per swab (median 1, range 0-8).

The largest group of isolates identified belonged to the Staphylococcus genus (66.4%, n=170) with *S aureus* being the most common species (17.9% n=46) of which 11% (n=5) were methicillin resistant. Further analysis of staphylococcal group is included in Figure 3.17. Corynebacteria made up 6.6% of isolates (n=17), with the most common species being *C*

auris (23.4% n=4), *C jeikeium* (17.6% n=3) and *C macginleyi* (17.6% n=3). Other species included *C propinquum* (n=2) and *C striatum* (n=2). Gram positive bacilli accounted for 7.8% (n=20) of the overall results and included brevibacterium (n=4), rhodococcus (n=4) and *Dermobacter hominis* (n=2). Gram negative bacilli accounted for 4.3% (n=11) isolates and included acinetobacter (n=2) and *brevundimonas* (n=2), *E coli* (n=1) and *Pseudomonas* spp (n=1). As with non-infected sites, the most frequently identified anaerobe was *P acnes* 4.3% (n=11) and *Clostridium* spp (1.95% n=5) (*C difficile*, *C perfringens*, *C sordelli 2*, *C sporogenes,* and *C subterminale*).

Figure 3.16 Bacteria from clinically infected pin sites

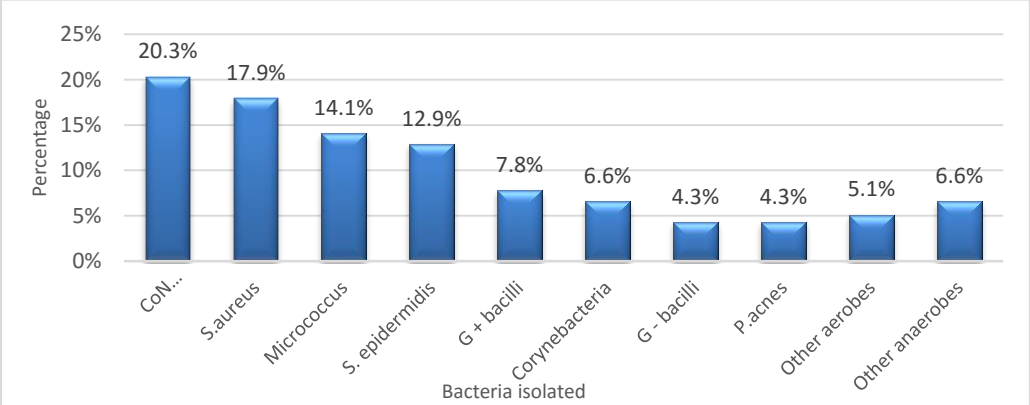
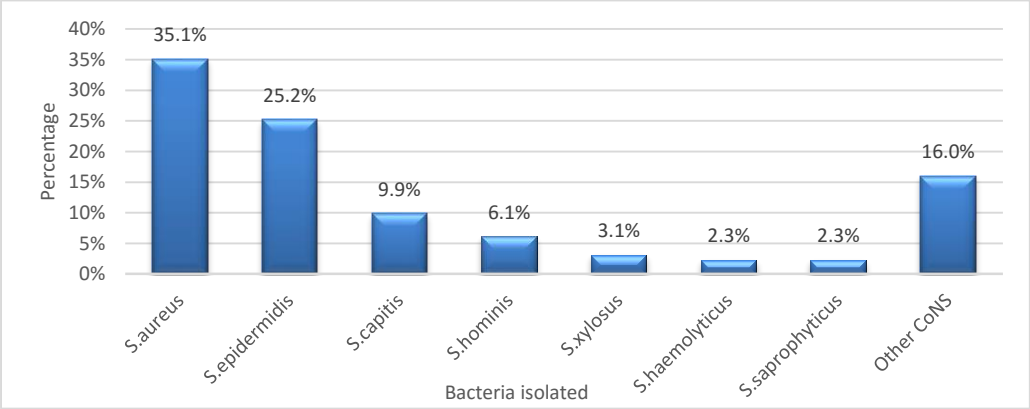


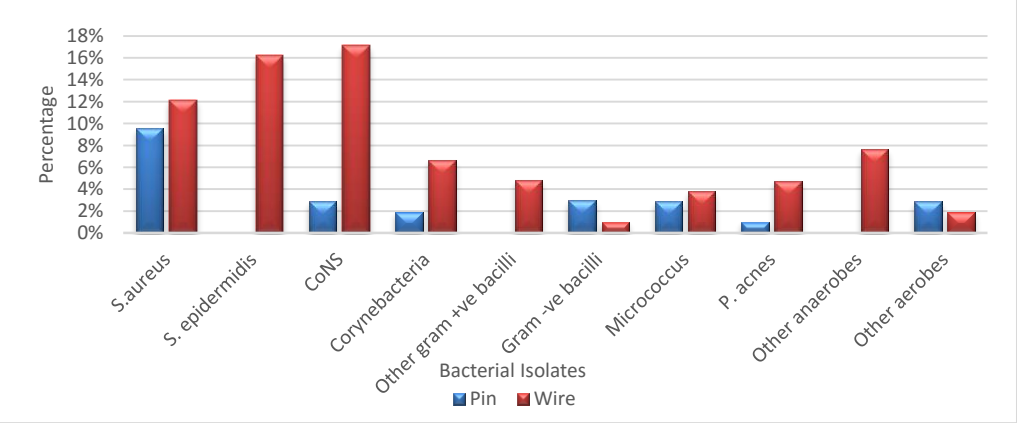
Figure 3.17 Staphylococci isolated from PSI



Eighty two swabs from 21 patients were included for further analysis using details of site of insertion and whether this was a pin or wire. No significant differences were identified in the type of bacteria identified at tibial sites (p=0.57). A small increase in the number of isolates was observed for proximal tibial sites compared to distal tibial sites with an average of 1.32 isolates per swab (median 1, range 0-6) (n=31) for proximal and 1.03 for distal sites (median 1, range 0-5) (n=29). Mid tibial sites had an average of 1.1 isolates per swab (median 1, range 0-4) (n=10) and wires to the foot had an average of 2.25 of isolates per swab (median 2, range 0-6) (n=8). Only 4 swabs were obtained from infected femoral pins, with an average of 0.8 isolates per swab (median 1, range 1-2).

Overall, 1.31 isolates were identified per swab (n=16) for tibial pins (median 1, range 0-5) and 1.13 for wires (median 1, range 0-6) (n=54). MANOVA identified statistically significant differences in bacteria isolated from pins and wires F (10, 60) = 2.022 p=0.046. Further univariate tests identified *S aureus* and *S epidermidis* as statistically different for pins and wires at F (1, 69) = 7.70, p=0.007 and F (1, 69) = 5.65, p=0.02 respectively. These results were confirmed using discriminate function analysis. A summary of bacteria identified from tibial pins and wires is presented in Figure 3.18.

Figure 3.18 Bacteria isolated from infected tibial pins and wires



3.4.1 Comparison of PSI and non PSI

Significantly more wires were infected than pins ($F(1,179) = 4.53$, $p=0.035$) and significant differences between PSI and non-PSI bacteria were observed ($F(11, 330) = 4.223$, $p < 0.001$). Univariate comparisons identified a statistical significance only for *S aureus* ($F(1, 340) = 42.94$, $p < 0.001$). Discriminate function analysis also identified *S aureus* as being a statistically significant predictor variable ($p<0.001$), with the other bacterial categories not being of statistical significance. Using the bacterial groupings, classification of PSI was correctly predicted in only 35.5%. This suggests that while *S aureus* is more common in PSI than non PSI, its presence alone is not an effective predictor of PSI.

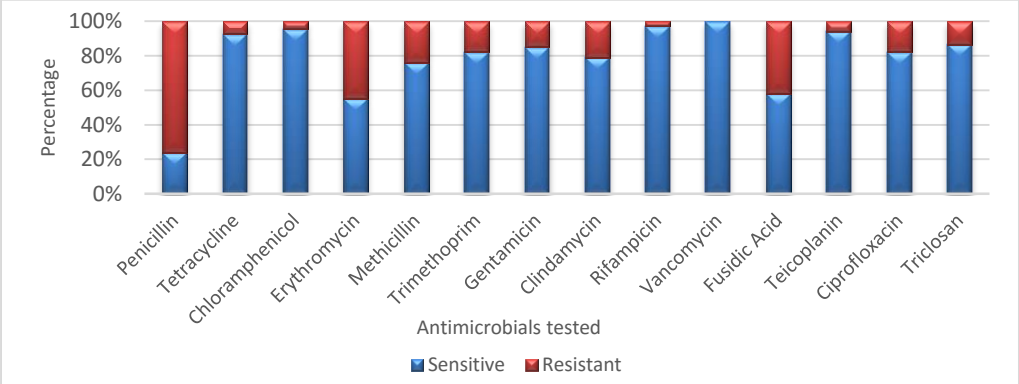
No significant differences were observed between PSI and site of tibial insertion ($F(1,179) = 0.37$, $p=0.85$) or bacteria identified at the site of insertion between PSI and non PSI isolates ($F(22,318) = 0.588$, $p=0.93$). No significant difference was identified overall between PSI and non PSI bacteria isolated from pins and wires using MANOVA ($F(11, 166) = 0.622$, $p=0.81$).

3.4.2 Antimicrobial sensitivity

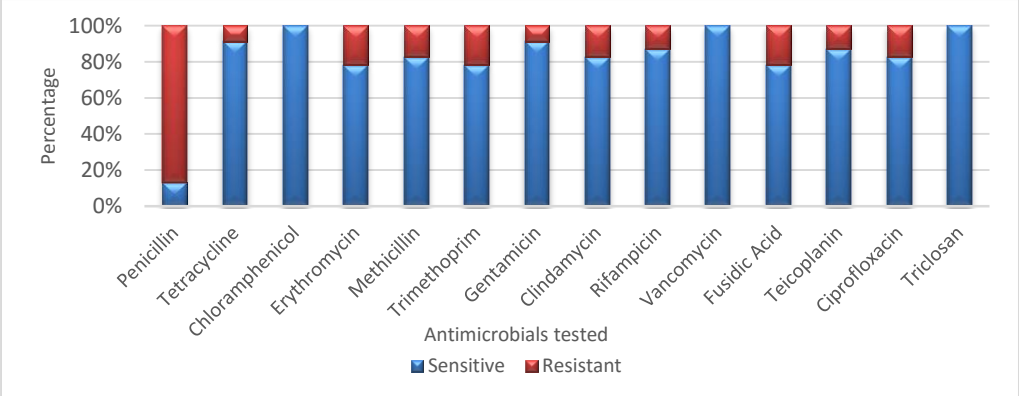
One hundred and fifty-six aerobic isolates from PSIs were tested for antimicrobial sensitives. Of the 126 gram positive cocci tested 78.9% were sensitive to clindamycin, 89.5% rifampicin and 79.7% triclosan. No isolates tested were resistant to all three antimicrobials used in the collar and 91.9% of isolates tested were sensitive to at least two of the antimicrobials. Sensitivity profiles for *S aureus*, CoNS and micrococci are shown in Figure 3.19

Figure 3.19 Bacterial sensitivity profiles

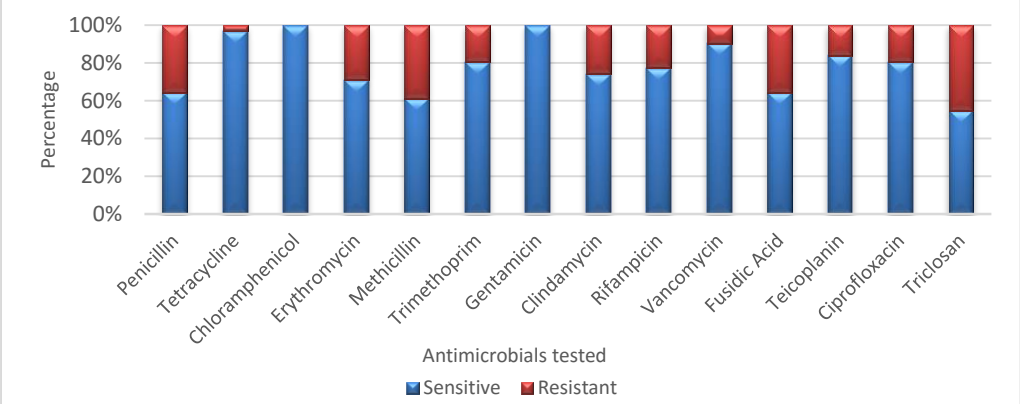
a) Sensitivity profiles of CoNS isolates (n=67)



b) Sensitivity profiles of *S aureus* isolates (n=23)



c) Sensitivity profiles of micrococci isolates (n=31)



Of the 15 corynebacteria tested only 7.7% were sensitive to clindamycin, 73.3% to rifampicin, and 33.3% to triclosan. Increased numbers of 'other' gram positive bacilli were sensitive to clindamycin (38.5%), although this was not of statistical significance ($p<0.05$). Rifampicin and triclosan sensitivities were 53.9% and 53.9% respectively.

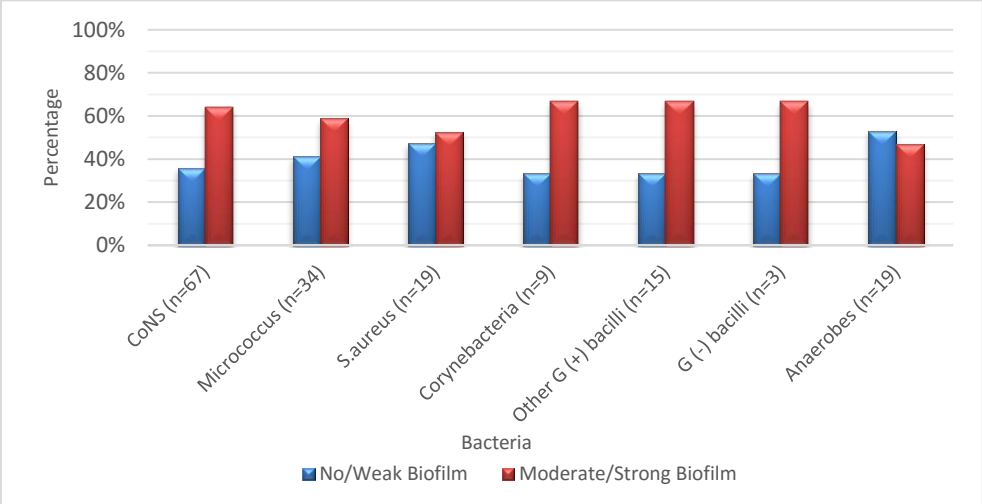
Only 20% corynebacteria were sensitive to two or more antimicrobials in the collar, whereas 53.8% of 'other' gram positive bacilli were sensitive to two or more antimicrobials. Of the gram negative bacilli tested 50% were sensitive to triclosan at 6.4mg/L.

Twenty-two anaerobe isolates were tested for sensitivity against the antimicrobials used in the collar. While 68.2% of isolates were sensitive to two of more of the antimicrobials, only 42.9% were sensitive to triclosan, 50% to rifampicin and 77.3% to clindamycin.

3.4.3 Biofilm capacity

Biofilm production of 168 PSI isolates was determined. Stepanović interpretation identified 19% isolates as non-biofilm producers, 20% weak, 33% moderate and 27% strong biofilm producers. Biofilm formation was observed for all bacterial categories, although no significant differences were noted between no/weak biofilm producers or moderate/strong biofilm producers ($p>0.05$) (Figure 3.20).

Figure 3.20 Biofilm production



3.5 Pre-clinical testing of collars

Test bacteria selected for pre-clinical testing are detailed in Table 3.1. They include *S aureus,* CoNS and corynebacteria to represent the most commonly identified organisms and included a typical antimicrobial sensitivity pattern of organisms identified.

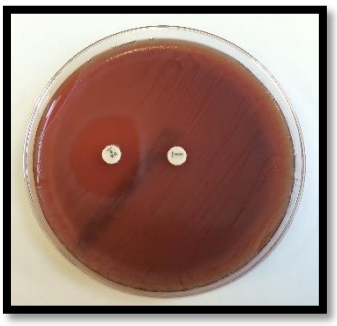
Table 3.1 Bacterial profiles and sensitivities

				MIC		
Freezer No.	**Organism**	**API profile**	**Antiobiogram profile**	**Rifampicin (mg/L)**	**Clindamycin (mg/L)**	**Triclosan (mg/L)**
F1693	*E coli*	5145552	76370	R	R	1.6
F2903	*S aureus*	6736153	40014	0.006	0.064	0.08
F2905	*Corynebacterium group G*	2100325	47624	0.002	R	6.4
F3412	*Corynebacterium jeikeium*	0100300	46120	0.23	0.094	R
F3451	*S epidermidis*	6706112	67024	0.008	0.19	0.1
F3501	*Corynebacterium macginleyi*	5100305	07224	0.16	R	R
F3592	*S aureus*	6734151	60720	0.75 *	2*	1.28

R=Resistant *=Above BSAC resistance breakpoint (BSAC 2015), indicating resistance

Inducible clindamycin resistance was elicited with F3451 (Figure 3.21). None of the other test strains demonstrated this trait.

Figure 3.21 F3451 (*S epidermidis*): Inducible resistance



Inducible resistance demonstrated by flattening of the ZoI around the clindamycin disc. This occurs when the *erm* gene, which encodes for resistance, is present and there is resistance to erythromycin.

Serial plate transfer test

SPTT was continued until Day 107. As results were read in triplicate the mean ZoI was calculated. No zones were detected for F3501 (*Corynebacterium group G*) at day 15 and day 48 for F3412 (*Corynebacterium jeikeium*). All other strains continued to demonstrate antimicrobial activity in excess of 3 months (Figure 3.22 Standard deviations presented in Appendix 13). Paradoxical resistance was noted on one sample of F1693 (*E coli*) at day 56 (Figure 3.23). No further signs of new bacterial resistance were observed. Larger zone sizes were apparent for strains with lower MICs. The control discs had no ZoI, indicating no antimicrobial activity of the silicone. The percentage change in zone diameter at Day 14, 29, 56 and 91 are presented in Table 3.2

Figure 3.22 SPTT for F2903, F3451, F1693, F2905, F3592, F3501 and F3412

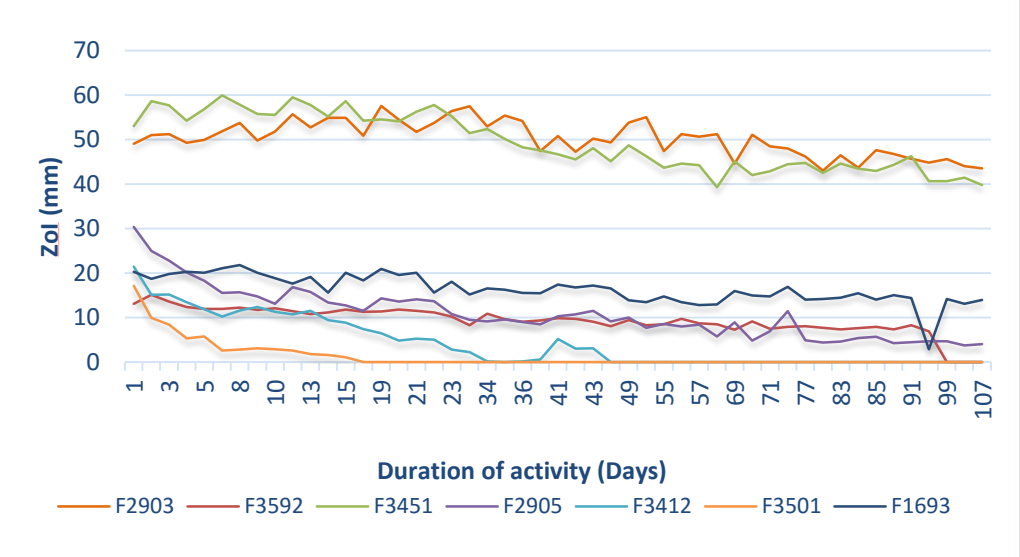
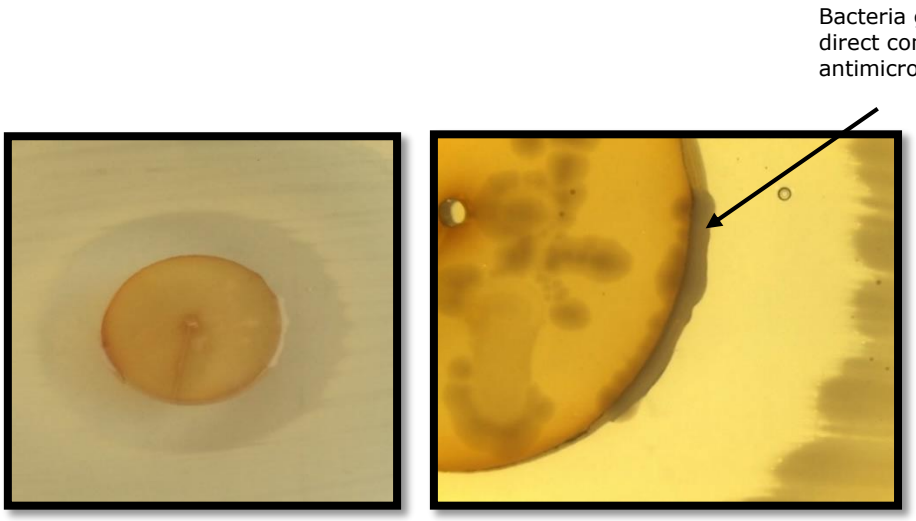


Figure 3.23 Paradoxical resistance on F1693 (*E coli*)



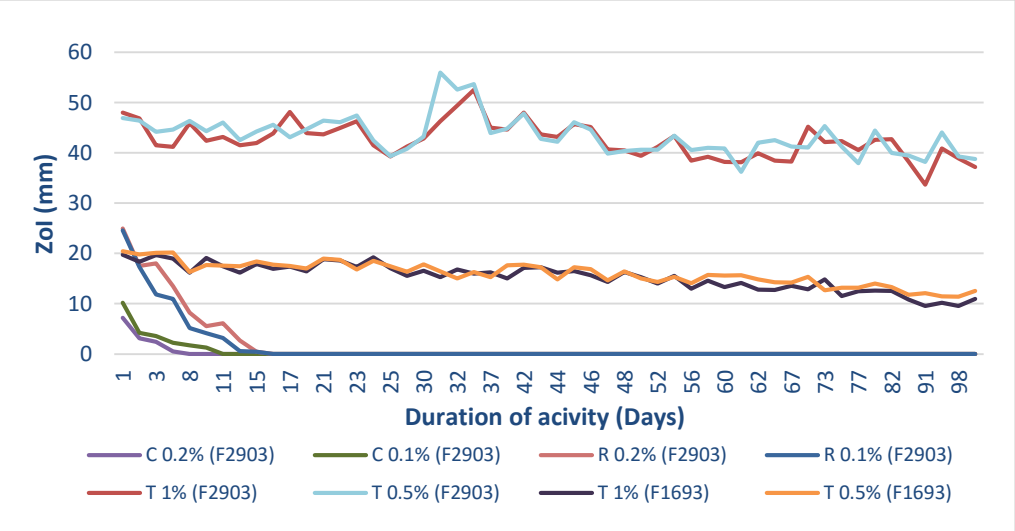
Antimicrobial collar tested with E coli showing a ZoI and bacteria growing in direct contact with the collar, indicating paradoxical resistance.

Table 3.2 Percentage difference in zone size from Day 1 SPTT ZoI for F2903, F3451, F1693, F2905, F3592, F3412 and F3501

	Change in zone size (%) compared to Day 1 (mm)						
Day	F2903	F3451	F1693	F2905	F3592	F3412	F3501
1	49.10mm	53.07mm	20.34mm	30.38mm	13.12mm	21.44mm	17.16mm
14	+11.83%	+ 4.00%	- 23.26%	- 55.96%	- 15.02%	- 55.97%	90.68%
29	+17.15%	- 3.03%	- 25.37%	- 68.57%	- 36.66%	- 89.46%	-
56	+ 4.32%	- 15.87%	- 33.68%	- 73.67%	- 25.99%	-	-
91	- 7.39%	- 12.81%	- 29.20%	- 85.22%	- 36.74%	-	-

SPTT results for individual drug impregnations are shown in Figure 3.24. (Standard deviations in Appendix 13). Triclosan discs (1% and 0.5%) maintained large zone sizes for 100 days. Percentage difference in zone size at day 14, 29, 56 and 91 are presented in Table 3.3. No statistically significant difference was observed between the 1% and 0.5% triclosan collars for F2903 (*S aureus*) (p=0.22) or F1693 (*E coli*) (p=0.19). Resistance occurred with clindamycin collars tested with F2903 at day 8 (0.2%) and Day 11 (0.1%), and at Day 16 for rifampicin (0.1% and 0.2%). No ZoI was evident for clindamycin and rifampicin discs with F1693 due to intrinsic resistance to these drugs in *E coli*.

Figure 3.24 SPTT with individual antimicrobials tested with F1693 and F2903



C = Clindamycin, R = Rifampicin, T = Triclosan

Table 3.3 Percentage difference in zone size from Day 1 SPTT with Triclosan 1% and 0.5% discs

	Change in zone size (%) compared to Day 1 (mm)			
	Triclosan 1%		Triclosan 0.5%	
Day	F2903 (*S aureus*)	F1693 (*E coli*)	F2903 (*S aureus*)	F1693 (*E coli*)
1	47.99mm	19.70mm	46.89mm	20.42mm
14	- 13.50%	- 17.82%	- 9.31%	- 14.69%
28	- 14.02%	- 21.22%	- 12.99%	- 19.74%
56	- 19.92%	- 33.96%	- 13.52%	- 31.15%
91	- 29.88%	- 50.36%	- 18.53%	- 40.79%

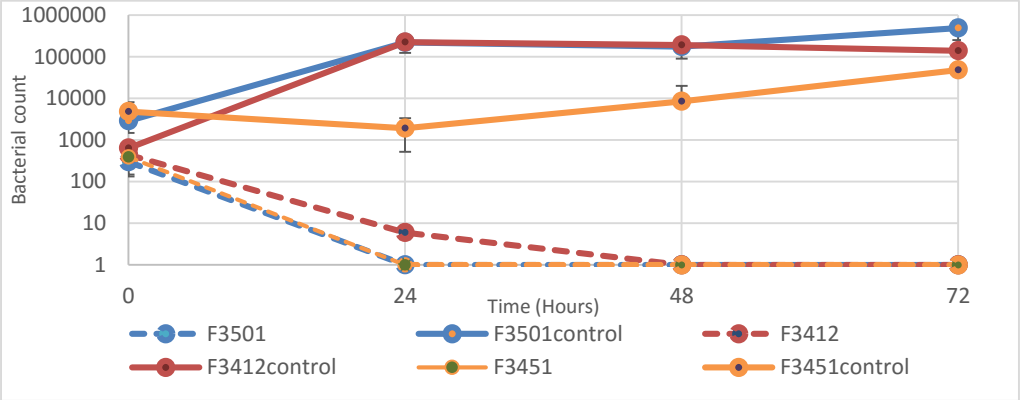
ZoI were significantly larger for discs with combined antimicrobials compared to single triclosan use when tested with F2903 ($p<0.001$). No significant differences of ZoI were detected with F1693 ($p=0.44$).

TK100

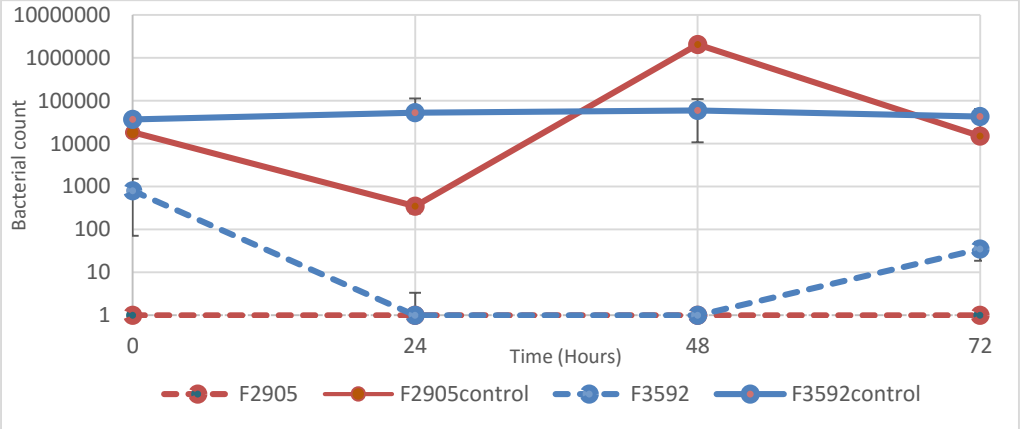
No viable bacteria were found at 24 hours using impregnated discs tested with F2903 (*S aureus*), F3351 (*S epidermidis*) and F3501 (*Corynebacterium jeikeium*). Strains F2905 (*Corynebacterium group G*) and F3412 (*Corynebacterium jeikeium*) were no longer viable at 48 hours and F1693 (*E coli*) at 72 hours (Figure 3.25). Strain F3592 (*S aureus*) did not kill all of the attached bacteria at 72 hours and regrowth of bacteria was evident with 35cfu/mL bacteria counted at 72 hours. The MIC was repeated for F3592 after exposure to the tK100 assay for 72 hours and the rifampicin MIC had increased from 0.75mg/L to 3mg/L, although no changes were observed for triclosan. Bacterial counts for the control discs remained constant, with the exception of F2905, although the cfu/mL remained higher than the impregnated discs throughout.

Figure 3.25 tK100 results

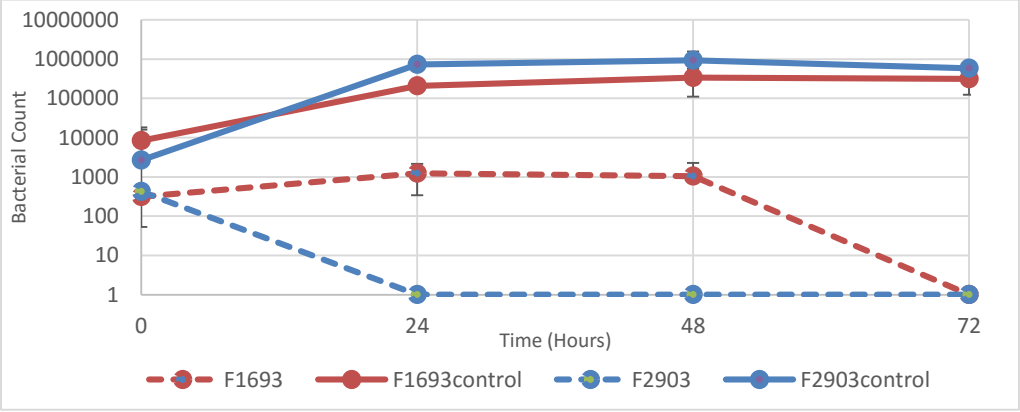
a) tK100 results for F3501 (*corynebacterium macginleyi*, F3412 (*Corynebacterium jeikeium*) and F3451 (*S epidermidis*)



b) tK100 results for F3592 (*S aureus*) and F2905 (*corynebacterium group G*)



c) tK100 results for F2903 (*S aureus*) and F1693 (*E coli*)



Pin track bacterial migration assay

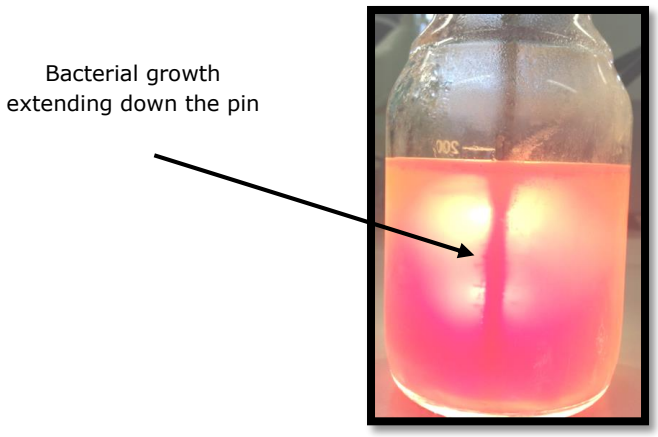
In preliminary tests no changes were evident in agar models with active collars until day 96 when one of the wire models showed colour change in the agar due to glucose fermentation (Figure 3.26). Following the weekly change of agar the same collar/wire failed at Day 104, and again at Day 111. No other changes were evident in pin or wire models using the antimicrobial collars. Bacterial growth was identified in the control models by Day 4 (Figure 3.27).

Figure 3.26 Bromocresol model using F2903 (*S aureus*)

Left: Bromocresol model with control collar. Colour change in the agar (yellow) is due to glucose fermentation, indicating the growth of bacteria.

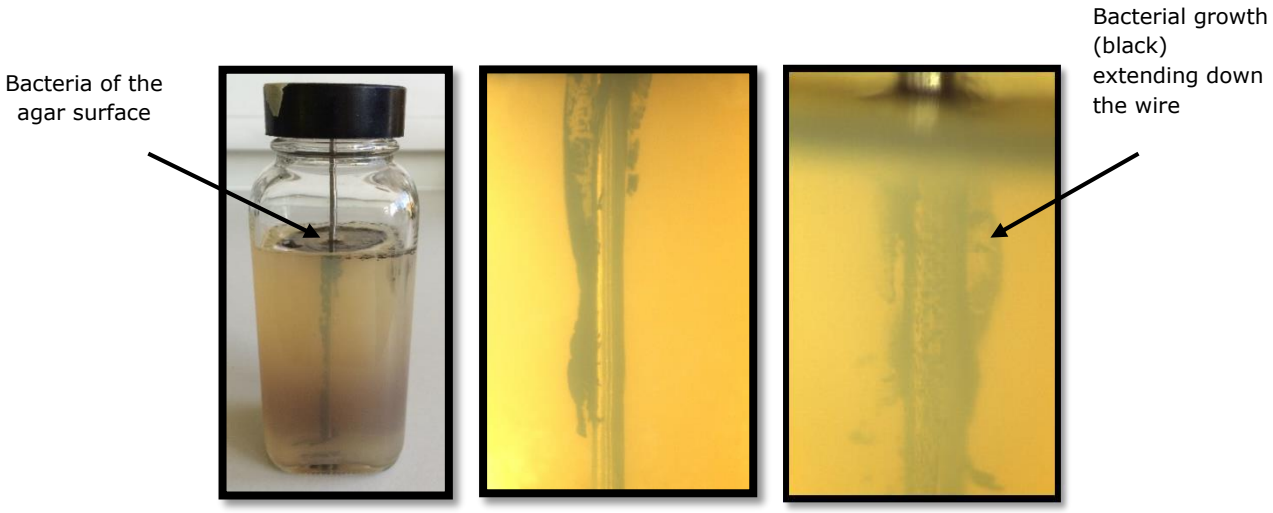
Right: Bromocresol model with antimicrobial collar. No change observed in agar colour (purple).

Figure 3.27 Bacterial growth along the pin in a control model using F2903 (*S aureus*)



In the final nutrient agar model F3592 (*S aureus*) tracked down control wires by 24 hours (Figure 3.28). Models with antimicrobial collars failed to prevent bacteria tracking down the wire, although did reduce bacterial growth in close proximity to the antimicrobial collar (Figure 3.29). Bacterial growth down the pin was less apparent in models without collars (Figure 3.31). This result occurred in triplicate on 3 separate occasions.

Figure 3.28 Nutrient agar control model (F3592, *S aureus*)



Nutrient agar model showing bacteria the surface of the agar (black), and extending down the wire (black).

Figure 3.29 Nutrient agar model with antimicrobial collar (F3592, *S aureus*)

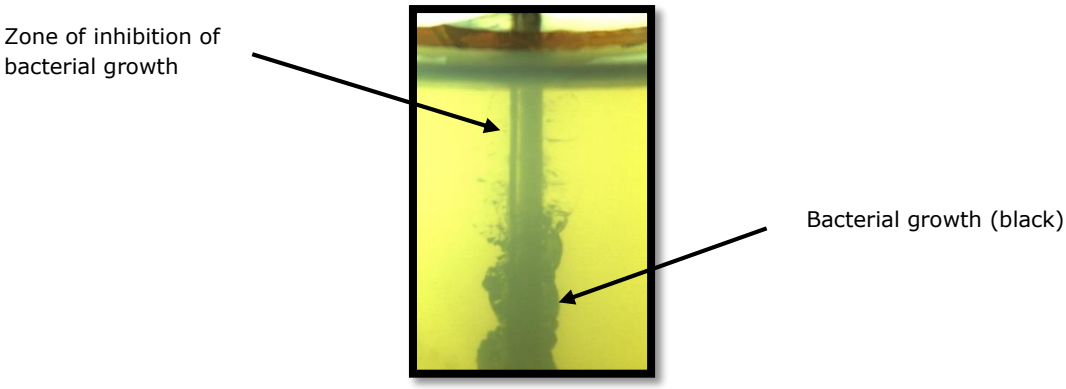


Figure 3.30: Nutrient agar model comparison (F3592, *S aureus*).

Left: Antimicrobial collar showed a zone of bacterial inhibition in close proximity to the collar, although was unable to prevent bacteria extending down the wire

Middle: Control (non-antimicrobial) collar did not prevent bacterial growth along the pin

Right: No collar control model showed less bacterial growth along the wire compared to antimicrobial collar or control (non-antimicrobial) collar

Models with F2903 revealed less growth down the pin track with the antimicrobial collar at Day 7 (Figure 3.31), although bacterial growth was still evident in close proximity of the collar. These results are consistent with previous sensitivity testing as F2903 has lower MICs to rifampicin and clindamycin than F3592.

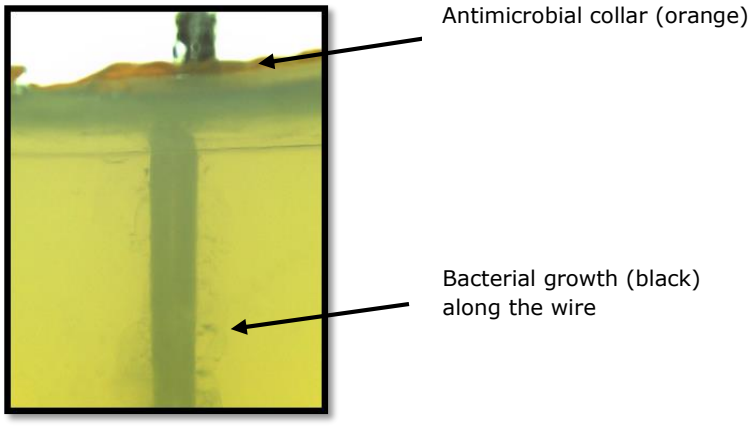
Figure 3.31 Nutrient agar model (F2903, *S aureus*)

a) Comparison of control (non-antimicrobial) collar and antimicrobial collar model

Left: Control (non-antimicrobial) collar model showing bacterial growth (black) on the agar surface and along the wire

Right: Antimicrobial collar model showing reduced bacterial growth

b) Nutrient agar model with antimicrobial collar (F2903, *S aureus*)



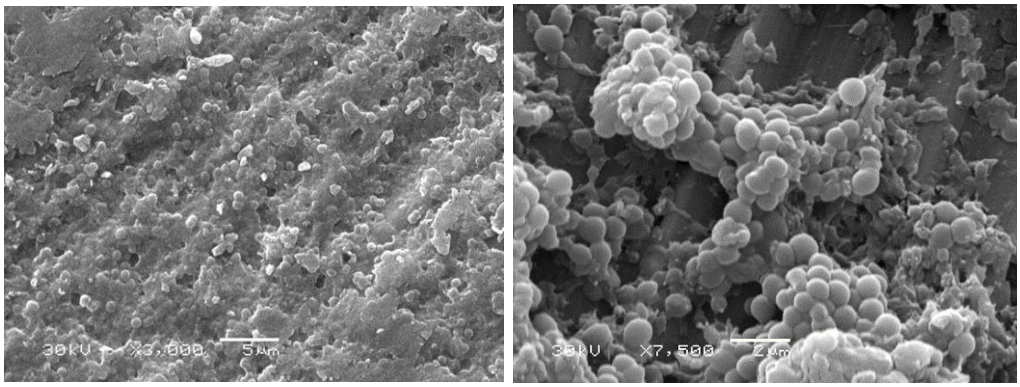
Nutrient agar model (F2903, *S aureus*) with antimicrobial collar showing reduced bacterial growth along the wire

Scanning Electron Microscopy

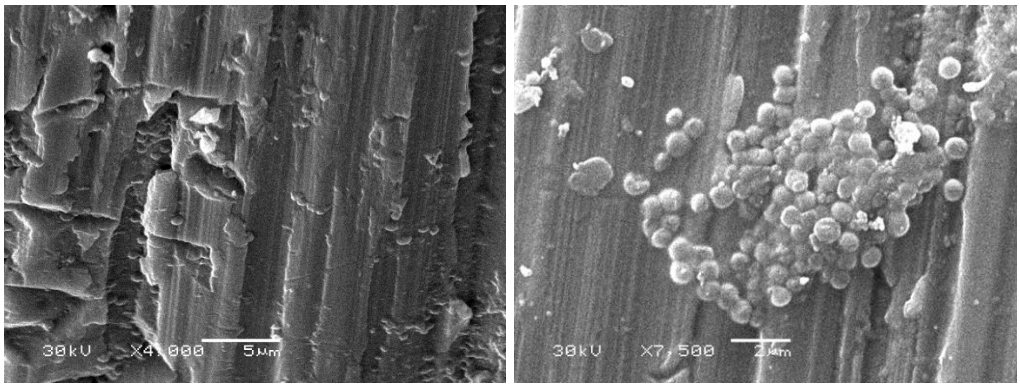
Wires from the pin track models F2903 and F3592 (both *S aureus*) were imaged using SEM. SEM images from model F2903 showed numerous bacteria on the control wire. Bacteria were also identified on the antimicrobial collar wire, although they were considerably more sparse (Figures 3.32). SEM images from F3592 wires did not appear to differ substantially in bacterial load between the control and antimicrobial collar wire.

Figure 3.32 SEM images of pin track model wire

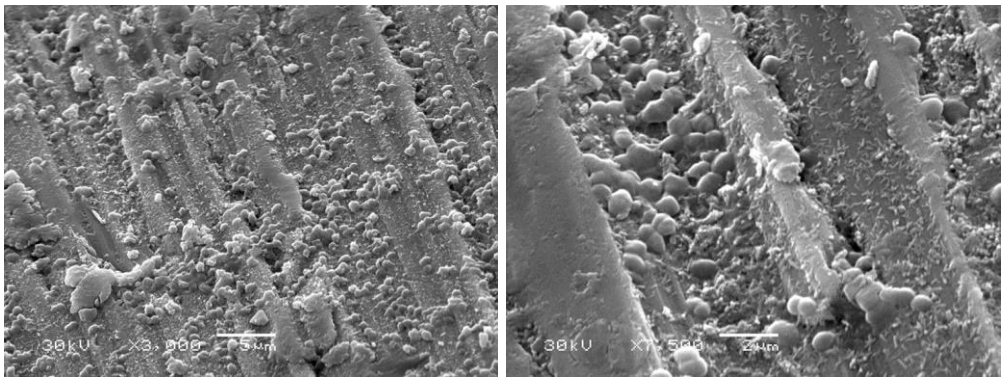
a) Wire from F2903 control model at x3000 and x7500 magnification



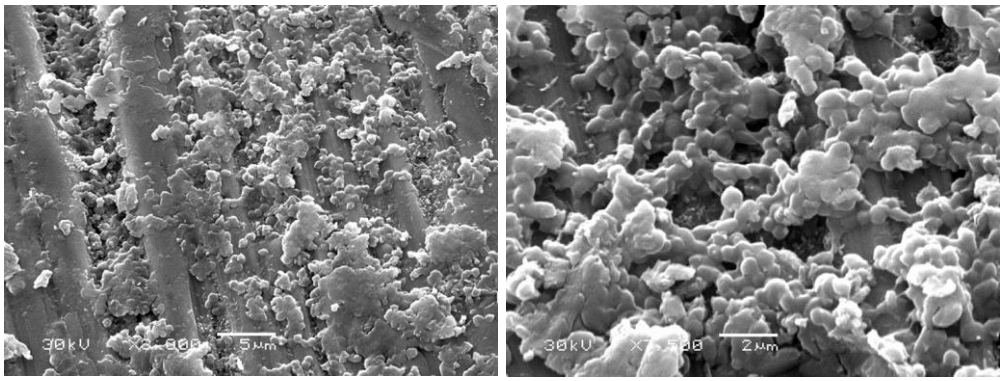
b) Wire from F2903 model with antimicrobial collar at x4000 and x7500 magnification



c) 3.49 Wire from F3592 control model at x3000 and x7500 magnification



d) Wire from F3592 model with antimicrobial collar at x3000 and x7500 magnification



Bacteria in images a, c and d appear to have an exopolysaccharide coating in contrast to image b.

HPLC

Figure 3.33 shows a typical chromatogram of clindamycin, rifampicin and triclosan. Calibration curves (Figure 3.34) were used to determine the antimicrobial content extracted from the silicone discs.

HPLC analysis was carried out over two sessions due to the number of samples to test. Neat samples were used for clindamycin and rifampicin and 1:10 dilutions for triclosan.

Figure 3.33 HPLC chromatogram using a wavelength of 201nm

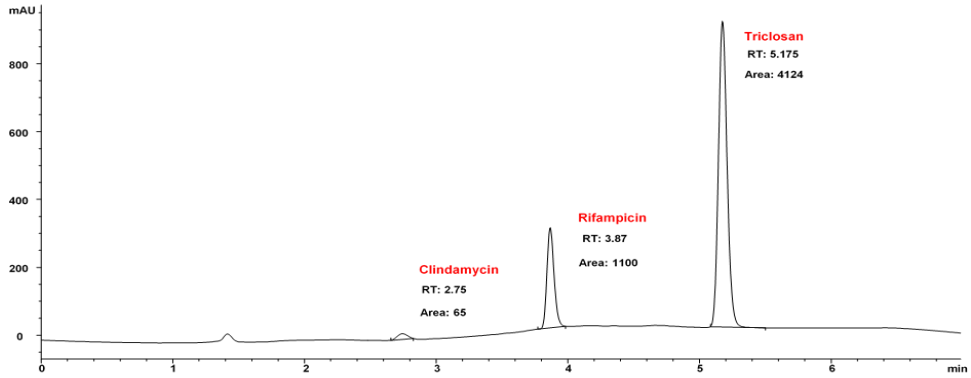
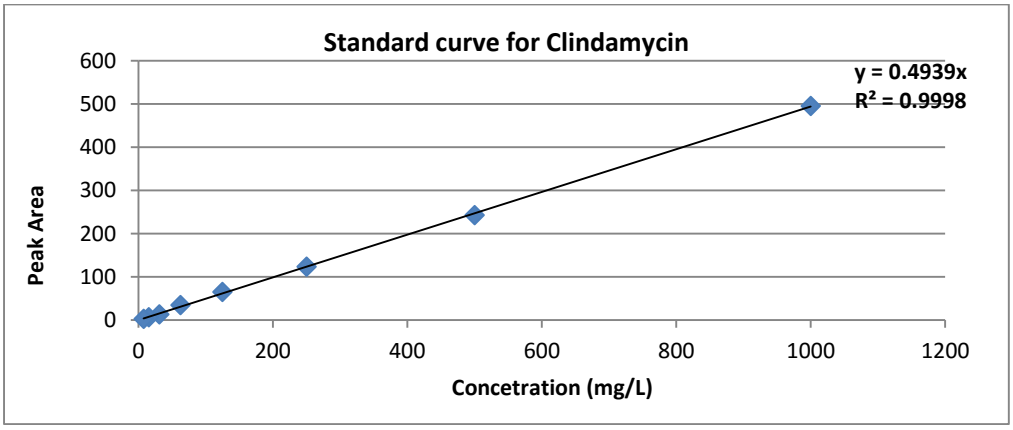
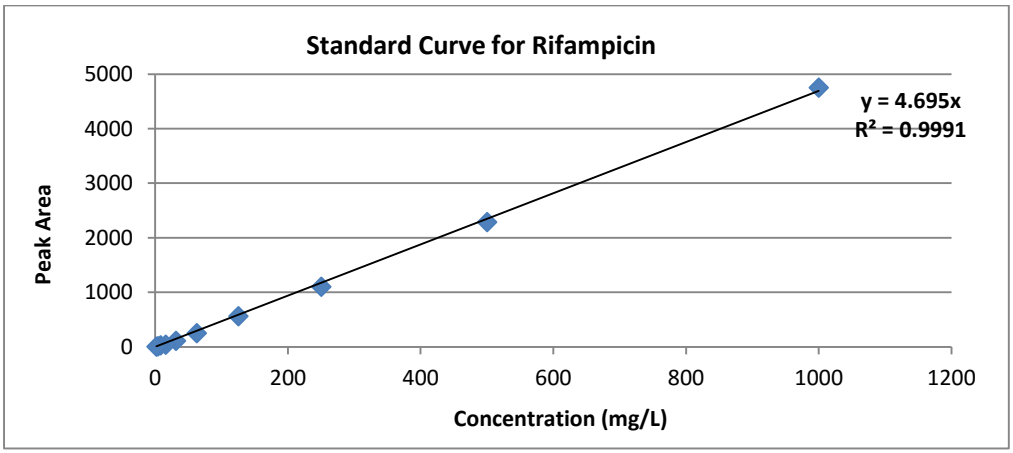


Figure 3.34 Standard calibration curves

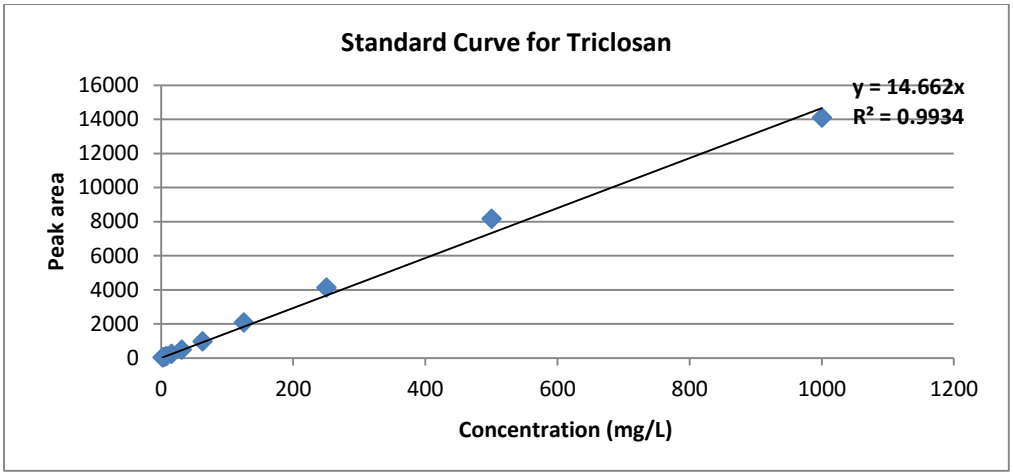
a) Standard calibration curve for clindamycin



b) Standard calibration curve for rifampicin



c) Standard calibration curve for triclosan



The drug content of each collar was calculated using the peak areas and the equation in Figure 3.35. The percentage of drug per disc (w/w) was also calculated. Average drug content per collar was 0.3mg clindamycin, 0.013mg rifampicin and 6.2mg triclosan in Batch 1 collars (Table 3.5). HPLC analysis of collars made using multiple impregnation methods showed that drug content steadily reduced with each impregnation, with a 46.7% reduction in clindamycin by Batch 5, 44.6% reduction in clindamycin and 46.6% reduction in triclosan.

Figure 3.35 Equation for drug content calculations

$$y = mx + c$$

Therefore $x = \frac{y+c}{m}$

y = peak area (Table x-x)
m = gradient of the straight line
x = drug concentration (µg/mL)
c = y intercept

Table 3.4 HPLC analysis of serial impregnation collars

a) HPLC analysis of Batch 1 collars

Batch 1		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	148.5	148.5	150.3	149.1	1.04	0.30	0.03
	Rifampicin	46.7	46.7	47.5	46.97	0.46	0.010	0.0011
	Triclosan	7813	7855	7820	7829.33	22.5	5.33	0.61
Collar B	Clindamycin	145.6	145.6	-	145.6	0	0.29	0.03
	Rifampicin	68.9	72.4	-	70.65	2.47	0.015	0.0017
	Triclosan	9301	9303	9299	9301	2	6.34	0.72
Collar C	Clindamycin	154.5	146.9	144.7	148.7	4.2	0.30	0.034
	Rifampicin	70.8	69.4	68.7	69.63	0.87	0.014	0.0017
	Triclosan	10152	10165	10175	10164	9.42	6.93	0.79

b) HPLC analysis of Batch 2 collars

Batch 2		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	123.8	123.6	122.4	123.27	0.76	0.24	0.028
	Rifampicin	37	40.3	40.4	39.23	1.93	0.0084	0.00095
	Triclosan	9036	9033	9045	9038	6.25	6.16	0.70
Collar B	Clindamycin	112.3	113.7	112.3	112.77	0.81	0.22	0.025
	Rifampicin	31.1	31.7	31	31.27	0.38	0.0067	0.00076
	Triclosan	8589	8611	8610	8603.33	12.42	5.86	0.67
Collar C	Clindamycin	84.9	85	85.9	85.27	0.45	0.17	0.019
	Rifampicin	33.9	34.4	34.1	34.13	0.21	0.007	0.0008
	Triclosan	10201	10223	10178	10200.67	18.37	6.95	0.79

c) HPLC analysis Batch 3 collars

Batch 3		**Peak area**			**Average**	**stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	108.1	109.6	111.3	109.67	1.60	0.22	0.025
	Rifampicin	79.2	79.1	79.5	79.27	0.21	0.016	0.0019
	Triclosan	77767	77764	7747	7759.33	10.79	5.29	0.60
Collar B	Clindamycin	96.5	88	92.5	92.33	4.25	0.18	0.021
	Rifampicin	238.2	234.8	235.4	236.4	1.82	0.05	0.0057
	Triclosan	7515	7519	7503	7512	8.33	5.12	0.58
Collar C	Clindamycin	72.1	67.8	67.4	69.1	2.13	0.13	0.016
	Rifampicin	239	237.7	237.3	238	0.73	0.05	0.0057
	Triclosan	8759	8784	8742	8761.67	17.25	5.97	0.68

d) HPLC analysis of Batch 4 collars

Batch 4		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	83.6	83.5	90.3	85.8	3.9	0.17	0.020
	Rifampicin	96.4	95.5	96.5	96.13	0.55	0.02	0.0023
	Triclosan	7243	7267	7229	7246.33	19.21	4.94	0.56
Collar B	Clindamycin	85.3	82.1	78.8	82.07	3.25	0.16	0.019
	Rifampicin	127.7	127.4	126.7	127.27	0.51	0.027	0.0031
	Triclosan	7108	7130	7113	7117	11.53	4.85	0.55
Collar C	Clindamycin	74.5	75.8	81.1	77.13	2.85	0.15	0.0017
	Rifampicin	130.8	131.8	132.4	131.67	0.66	0.028	0.0032
	Triclosan	6708	6690	6694	6697.33	7.72	4.56	0.52

e) HPLC analysis of Batch 5 collars

Batch 5		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	93.5	91.5	92.6	92.53	1.00	0.18	0.021
	Rifampicin	36.5	36.9	37.7	37.03	0.61	0.0078	0.0009
	Triclosan	5239	5234	5214	5229	13.23	3.56	0.40
Collar B	Clindamycin	85.1	85.6	85.5	85.4	0.27	0.17	0.020
	Rifampicin	51.3	51.5	51.4	51.4	0.01	0.01	0.0012
	Triclosan	5076	5040	5056	5057.33	18.04	3.44	0.39
Collar C	Clindamycin	72.8	76.5	75.7	75	1.59	0.15	0.017
	Rifampicin	18.6	18.9	19	18.83	0.17	0.004	0.0005
	Triclosan	4331	4320	4323	4324.67	4.64	2.94	0.33

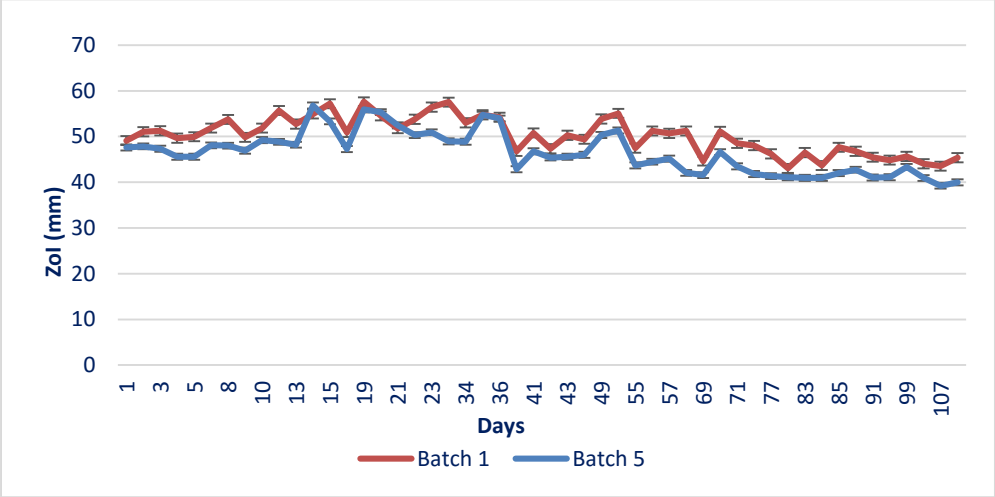
Due to the evaporation of chloroform during the impregnation process, the post-impregnation samples showed a higher concentration of antimicrobials per mL than pre-impregnation samples (Table 3.5). After each impregnation the evaporated chloroform was replaced, returning the antimicrobial solution to the original volume (100mL). Analysis of the reconstituted impregnation solution showed a gradual decline in drug concentration with each batch impregnated.

Table 3.5 HPLC analysis of impregnation solution

Solutions		**Peak area**			**Average**	**Stdev**	**% Drug concentration per 1mL**	**Drug content Per mg/ml**
		Sample 1	Sample 2	Sample 3				
Pre-B1	Clindamycin	75.4	75	75	75.13	0.23	100%	2mg
a	Rifampicin	660	660	655	658.33	2.89	100%	2mg
	Triclosan	3981	3961	3961	3967.67	11.55	100%	10mg
Post-B1	Clindamycin	88	88	88	88	0	117.12%	2.34mg
b	Rifampicin	763	762	761	762	1	115.74%	2.31mg
	Triclosan	4614	4575	4572	4587	23.43	115.60%	11.56mg
Pre-B2	Clindamycin	72	71	72	71.67	0.58	95.38%	1.96mg
c	Rifampicin	623	625	624	624	1	94.78%	1.89mg
	Triclosan	3769	3745	3733	3749	18.33	94.23%	9.42mg
Post-B2	Clindamycin	89	90	89	89.33	0.58	118.89%	2.37mg
d	Rifampicin	760	761	762	761	1	115.74%	2.31mg
	Triclosan	4025	4021	4000	4015.33	13.43	101.20%	10.12mg
Pre-B3	Clindamycin	73	73	-	73	0	97.16%	1.94mg
e	Rifampicin	616	616	-	616	0	93.56%	1.87mg
	Triclosan	3492	3487	3487	3488.67	2.89	87.97%	8.79mg
Post-B3	Clindamycin	80.4	80	-	80.2	0.28	106.7%	2.13mg
f	Rifampicin	691	691	-	691	0	104.96%	2.09mg
	Triclosan	3519	3512	3503	3511.33	8.02	88.49%	8.84mg
Pre-B4	Clindamycin	74	75	74	74.33	0.58	98.93%	1.97mg
g	Rifampicin	647	644	644	645	1.73	97.97%	1.95mg
	Triclosan	3135	3122	3106	3121	14.52	78.66%	7.86mg
Post-B4	Clindamycin	81	80	80	80.33	0.58	106.92%	2.13mg
h	Rifampicin	707	706	707	706.67	0.58	107.34%	2.14mg
	Triclosan	3360	3346	3346	3350.67	8.08	84.44%	8.44mg
Pre-B5	Clindamycin	64	64	64	64	0	85.18%	1.70mg
i	Rifampicin	569	569	567	568.33	1.15	86.32%	1.72mg
	Triclosan	2660	2637	2633	2643.33	14.57	66.62%	6.66mg
Post-B5	Clindamycin	70	69	70	69.67	0.58	92.72%	1.85mg
j	Rifampicin	595	592	594	593.67	1.5	90.17%	1.80mg
	Triclosan	2813	2798	2793	2801.33	10.41	70.76%	7.07mg

No signs of bacterial resistance were observed with Batch 1 or 5 of the antimicrobial collars during the SPTT period of 115 days. SPTT results from Batches 1 and 5 collars are presented in Figure 3.36.

Figure 3.36 SPTT results for Batch 1 and Batch 5 collars (F2903, *S aureus*)



A statistically significant difference in zone size was detected using a 2 tailed t-test ($p<0.01$), though as both discs maintained substantial zones sizes throughout the experiment (Figure 3.37), this may not be of clinical consequence. The percentage change in zone sizes at Day 14, 29, 56 and 91 are presented in Table 3.6

Figure 3.37 SPTT plates for Batch 1 (left plate) and Batch 5 (right plate) using F2903

a) Day 92 b) Day 114

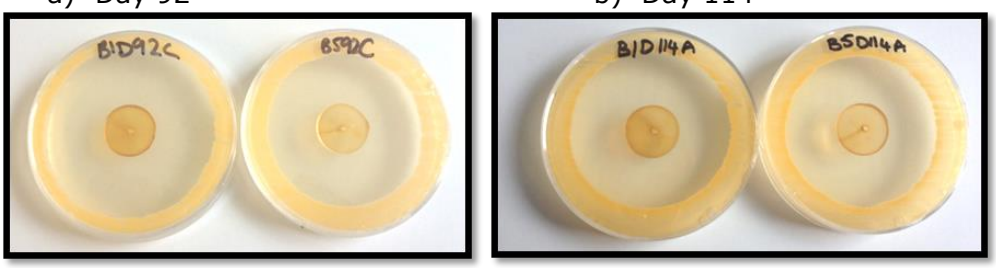


Table 3.6 Percentage change in zone size for Batch 1 and Batch 5 collars tested with F2903 (*S aureus*)

	Change in zone size (%) compared to Day 1 (mm)	
Day	Batch 1 collar	Batch 5 collar
1	49.10mm	47.60mm
14	+11.83%	+ 11.98%
29	+17.15%	+ 2.84%
56	+ 4.32%	- 6.53%
91	- 7.39%	- 13.76%

HPLC analysis of drugs extracted from Batch 1 and Batch 5 collars after SPTT are included in Tables 3.7

Table 3.7 HPLC analysis of Batch 1 and Batch 5 collars after SPTT (F2903, *S aureus*)

a) Batch 1 collars after SPTT (F2903 S aureus)

SPTT B1 Isolate F2903		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	27.4	23	22.2	24.2	2.8	0.048	0.0056
	Rifampicin	10	5	6	7	2.64	0.0014	0.00017
	Triclosan	4247	4254	4250	4250.33	3.51	2.89	0.33
Collar B	Clindamycin	33	26	24	27.67	4.73	0.056	0.0064
	Rifampicin	23	22	24	23	1	0.0048	0.00056
	Triclosan	4167	4162	4146	4158.33	10.97	2.83	0.32
Collar C	Clindamycin	27.1	29.4	13.3	23.27	7.1	0.047	0.0054
	Rifampicin	11.7	19.7	-	15.7	4	0.0033	0.00038
	Triclosan	3853	3832	3833	3839.33	9.67	2.61	0.30

b) Batch 5 collars after SPTT (F2903 *S aureus*)

SPTT B5 Isolate F2903		**Peak area** Sample 1	Sample 2	Sample 3	**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
Collar A	Clindamycin	20.5	22.2	21.4	21.37	0.85	0.04	0.0049
	Rifampicin	42.1	41.7	64.8	49.43	13.22	0.01	0.0012
	Triclosan	2463	2453	2451	2455.67	6.43	1.67	0.19
Collar B	Clindamycin	55.1	54	55.1	54.73	0.64	0.11	0.013
	Rifampicin	41.2	41.4	40.9	41.17	0.25	0.008	0.0010
	Triclosan	2371	2370	2343	2361.33	15.89	1.61	0.18
Collar C	Clindamycin	67	64.3	66	65.77	1.12	0.13	0.015
	Rifampicin	41.5	41.3	41.3	41.37	0.09	0.008	0.0010
	Triclosan	2321	2325	2343	2329.67	9.57	1.58	0.18

HPLC Analysis following in-vitro testing

Drug content was markedly reduced following the SPTT and pin track experiments using Batch 1 collars. Clindamycin and rifampicin were not detected in any of the samples, although triclosan was identified in all samples. An average of 3.75mg triclosan was released during SPTT, representing a 60.5% decrease. HPLC results are presented in Table 3.8 and 3.9

Table 3.8 HPLC analysis of Batch 1 collar after SPTT

a) HPLC analysis of Batch 1 collar after SPTT (F2905, Corynebacterium group G)

SPTT Isolate F2905		**Peak area** Sample 1	Sample 2	Sample 3	**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
Collar A	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	447	448	427	440.67	11.84	3.00	0.34
Collar B	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	337	338	337	337.33	0.58	2.30	0.26
Collar C	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	342	343	342	342.33	0.58	2.33	0.27

b) HPLC analysis of Batch 1 collar after SPTT (F1693 *E coli*)

SPTT Isolate F1693		**Peak area** Sample 1	Sample 2	Sample 3	**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
Collar A	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	228	228	229	228.33	0.58	1.55	0.18
Collar B	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	356	357	358	357	1	2.43	0.28
Collar C	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	320	319	320	319.67	0.58	2.18	0.25

c) HPLC analysis of Batch 1 collar after SPTT (F3451, *S epidermidis*)

SPTT Isolate F3451		**Peak area** Sample 1	Sample 2	Sample 3	**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
Collar A	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	463	462	461	462	1	3.15	0.36
Collar B	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	373	375	373	373.67	1.16	2.54	0.29
Collar C	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	435	433	437	435	2	2.96	0.34

d) HPLC analysis of Batch 1 collar after SPTT (F3592, *S aureus*)

SPTT Isolate F3592		**Peak area** Sample 1	Sample 2	Sample 3	**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
Collar A	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	376	377	378	377	1	2.57	0.29
Collar B	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	438	439	438	438.33	0.58	2.98	0.34
Collar C	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	403	404	404	403.67	0.58	2.75	0.31

d) HPLC analysis of Batch 1 collar after SPTT (F3412, *Corynebacterium jeikeium*)

SPTT Isolate F3412		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	293	294	294	293.67	0.58	2.00	0.23
Collar B	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	245	245	246	245.33	0.58	1.67	0.19
Collar C	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	-	-	-	-	-	-	-
	Triclosan	208	208	209	208.33	0.58	1.42	0.16

Table 3.9 HPLC analysis of Batch 1 collar after pin track testing with F2903 (*S aureus*)

Pin Isolate F2903		**Peak area**			**Average**	**Stdev**	**Drug content Per disc (mg)**	**% drug per disc**
		Sample 1	Sample 2	Sample 3				
Collar A	Clindamycin	15.8	13.9	14.1	14.6	1.04	0.029	0.0034
	Rifampicin	13.5	12.8	12.9	13.07	0.38	0.002	0.00032
	Triclosan	808	816	816	813.33	4.62	0.55	0.06
Collar B	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	57.7	58.1	57.9	57.9	0.2	0.012	0.0014
	Triclosan	3069	3102	3093	3088	17.06	2.10	0.24
Collar C	Clindamycin	-	-	-	-	-	-	-
	Rifampicin	53.8	53.7	53.8	53.77	0.05	0.011	0.0013
	Triclosan	3359	3362	3351	3357.33	4.64	2.28	0.26

3.6 Clinical testing of antimicrobial collars

3.6.1 Patient and public involvement

Study design

Only two members of the NUH PPI group were willing to participate in a focus group to discuss the project. Reasons for members declining the invitation were primarily related to the specialist nature of the research and perceived inability to contribute due to lack of experience and knowledge in the research area. No further volunteers were identified via NUH communications team or CLARCH. Due to insufficient numbers of interested parties a focus group was not scheduled.

Collar design

Fifty people were interviewed regarding the concept, acceptability, usability and any aspects of the collar which they thought would be challenging or problematic. The sample group included patients (n=4), public (n=7), doctors (n=5), nurses (n=23), occupational therapists (n= 2), orthotists (n= 1), physiotherapists (n= 1) and undergraduate nursing students (n= 7). Of those surveyed 98% (n=49) responded positively towards the collar citing that the collar would be easy to use and might be a better method than that currently used. Respondents favoured the longevity of the collar and the novel principle that it can be washed and replaced. Positive responses are summarised in Table 3.10.

Table 3.10 Positive comments on the antimicrobial collar

Comment	**Number (%)**
Good idea	n=48 (96%)
Easy to use	n=33 (66%)
Like the idea of being able to wash and replace	n=11 (22%)
Would be happy to use as a patient	n=6 (12%)
Length of time that they can be used for	n=4 (8%)
Quicker to use than gauze	n=3 (6%)
Better appearance than gauze	n=2 (4%)
I like the concept. It is difficult to clean the back (halo) pins properly and this will help	n=2 (4%)
Practical	n=2 (4%)
Better for patients	n=1 (2%)
Expect it to be an effective strategy to reduce PSI	n=1 (2%)
Good size - fits pins and wires well	n=1 (2%)
Much better to use than gauze as less 'fiddly'	n=1 (2%)
Neat	n=1 (2%)
Provides a good barrier	n=1 (2%)
Like size of collars	n=1 (2%)
Good alternative to Biopatch®	n=1 (2%)

Concerns were raised by 30% (n=15) and were divided into two main themes: concern for skin integrity, and fit of the collar. Concerns of skin integrity were due to the non-absorbent properties of the collar, and the concern that any moisture under the collars could lead to maceration of the skin, and potentially be detrimental to the pin site. Concerns regarding the fit of the collar were mainly due to the initial placement of collars between wires, and if the material would stretch or fall off after prolonged use. Potential problems and concerns are summarised in Table 3.11.

Table 3.11 Potential Problems or concerns of the antimicrobial collar

Comment	**Number (%)**
Skin may become macerated underneath the collar	n=7 (14%)
Are they likely to fall off?	n=3 (6%)
Will leaking pins compromise skin integrity as collars lack absorbing properties?	n=3 (6%)
Appropriateness of antimicrobial combination	n=1 (2%)
Are there enough PSI's to warrant use?	n=1 (2%)
Can they fit in small gaps between the wires/ can they be trimmed to fit?	n=1 (2%)
Possible corkscrewing of collar on pin due to the pin thread	n=1 (2%)
Possible local reaction to the collar	n=1 (2%)
Sizing of the collars – will they stretch?	n=1 (2%)
The skin is likely to become 'hot and sweaty' underneath the collar	n=1 (2%)
What about when pins are leaking? Can they be used with dressings?	n=1 (2%)

Several general comments were made during the interview process, and these have been summarised in Table 3.12. Positive suggestions for product development and future use were also considered by several respondents and these have been summarised in Table 3.13.

Table 3.12: General comments on the antimicrobial collar

Comment	**Number (%)**
No concerns	n=30 (60%)
Consideration of cost	n=2 (4%)
Good idea, unless they fall off	n=1 (2%)
Unlikely to fall off	n=1 (2%)
Would wards have stock available to replace any that fall off pins?	n=1 (2%)
What is the best timing of application?	n=1 (2%)

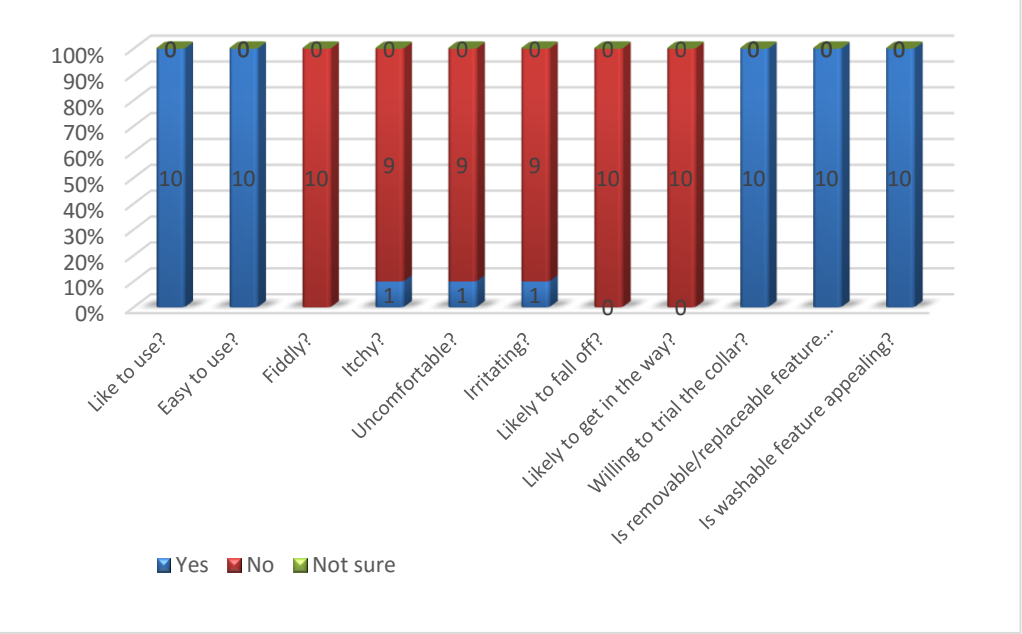
Table 3.13 Suggestions for improvements to the antimicrobial collar

Comment	**Number (%)**
Do they need a clip on to keep discs are flush next to the posterior halo pins due to hair creating a barrier?	n=1 (2%)
Do they need an absorbable under layer?	n=1 (2%)
Good idea - could these be used for central venous catheters?	n=1 (2%)

Service user evaluation of prototype collars

Ten service users with external fixator devices appraised sterilised (non-impregnated) prototypes of the collars and provided feedback on their use. All patients approached were willing to test the collar. Of those surveyed all thought that the collar would be easy to use and would be willing to use the collar either as part of normal care or as part of a clinical trial. When asked how easy the collar would be to use and replace, all respondents responded 'very easy' or 'easy'. Of those surveyed, no-one thought the collar would be 'difficult' or 'very difficult' to apply. Only one patient found the collar to be itchy and irritating, although this patient was also under the care of the dermatology team for contact dermatitis. The removable/replaceable and washable feature of the collar was thought to be a positive feature by all respondents. Results are summarised in Figure 3.38

Figure 3.38 Service user evaluation of prototype collars



The unstructured feedback on the collars again was largely positive with the collars being perceived as a better way of managing pin sites than the current methods used. This has been summarised in Table 3.14. Overall respondents were happy with the design of the collar and would use the current design of the prototype. Several suggestions were made for possible improvements such as changing shapes and colours to appeal to children, or changing the texture of the collar to make it 'foamy' for added comfort. Free comments identified that the 3mm collars trialled during the consultation did not always sit flat on the skin, either due to the contour of the leg, or due to the fact that pins were not all inserted at a 90° angle to the skin.

Table 3.14 Service user qualitative responses on prototype collars

Question lead	Response and respondent number
Would it be easy to use?	• Fairly easy to use – not that difficult. Will be easier to use as the treatment goes on (4) • Yes, but good dexterity will be needed (3) • Yes, as you can slot on to the pin and slide it to the skin even if you cannot reach the pin (1) • Yes, easier than using gauze (5)
Is it itchy?	• No, it's better than gauze (3)
Is the fact that it is washable appealing?	• Yes, it's better for the environment than keep using gauze (6)
What do you like about the collar?	• Like the simplicity (7, 9, 10) • Easy to use – better than gauze (5, 10) • Cooling effect around the pin site (7) • Covers the entry sites so less to look at, which is better (2) • Covers the pin site and stops contamination (2) • Covers pin sites. You can leave it on and have a barrier against germs till you clean your pin sites next time. It is easy to apply (4) • Easy to fit, less to think about, leg looks cleanser and more tidy. (5) • I like the fact that they cover the pin insertion site (4) • Less 'tickly' than gauze. More practical and easier to use, will need the nurse to visit at home less often to carry out pin site care (6) • More comfortable than gauze (3) • The collars are easier to use than gauze; they look better and are better for the environment. (6)
What do you dislike about the collar?	• Nothing (2, 3, 4, 5, 6, 7, 8, 9, 10)
What would you change?	• Nothing (1, 2, 4, 6, 7, 8,9,10) • As the leg 'expands and contracts' collars may not sit flush to the skin – could you use something with a creeping movement? (1) • Make it 'foamy' (5) • Possibly have different shapes/ colours or motifs to appeal to children (7) • Shape to fit the contours of the leg (3)
Other free comments and thoughts	• How will they absorb the leaking in the first 72 hours? Should they be used at the start? (1) • Large diameter too difficult to get two collars close together (2) • Pins are not inserted at a straight angle, so collars will not sit straight (1) • The collar does not sit flat on the skin (1) • Will the collar work if I use moisturiser? Will it form a barrier? (3)

Collar thickness

Twenty members of staff and public were asked about their preferred thickness of collar. Of those surveyed, 65% preferred the 2mm thickness, 30% 1mm, and 5% 3mm thickness. Reasons were predominantly based on personal preferences. Questions were raised regarding efficacy of different thicknesses, or the possibility of having different thicknesses for different pin sites. The majority of those surveyed were under the age of 60 years and did not suffer from any difficulties with manual dexterity. One service user was over 70 years of age, and though did not struggle to apply the collars did highlight the more insubstantial nature of the 1mm and 2mm. It was emphasized that the thickness of a 3mm collar would be sturdy enough to handle and apply, even with some loss of dexterity. A summary of the free comments regarding collar thickness is included in Table 3.15.

Table 3.15 Perspectives on collar thickness

Additional comments and respondent number
• 1mm too flimsy (2, 6, 7, 8, 13, 14, 16, 17, 20) • 3mm too thick (2, 5, 8, 10, 14, 16, 17, 20) • 1.5mm would be preferred (6,7) • 1mm thickness less obvious (19) • 1mm allows pins to be more visible without removing the collar (5) • 1mm thickness might fall off the pin (13) • 1mm thickness would be less 'hot and sweaty' to wear (18) • Could you have different thickness for different sites – 2mm for external fixators, 1mm for halo pins (9) • 3mm would be easier for patients with poor manual dexterity (12) • Would 1mm thickness be as effective as 2mm/3mm? (1) Health care professional response: 1, 3, 4, 5, 7, 8, 9, 10, 11, 16, 17, 20 Patient or public response: 2, 6, 12, 13, 14, 15, 18, 19

3.6.2 Feasibility Study

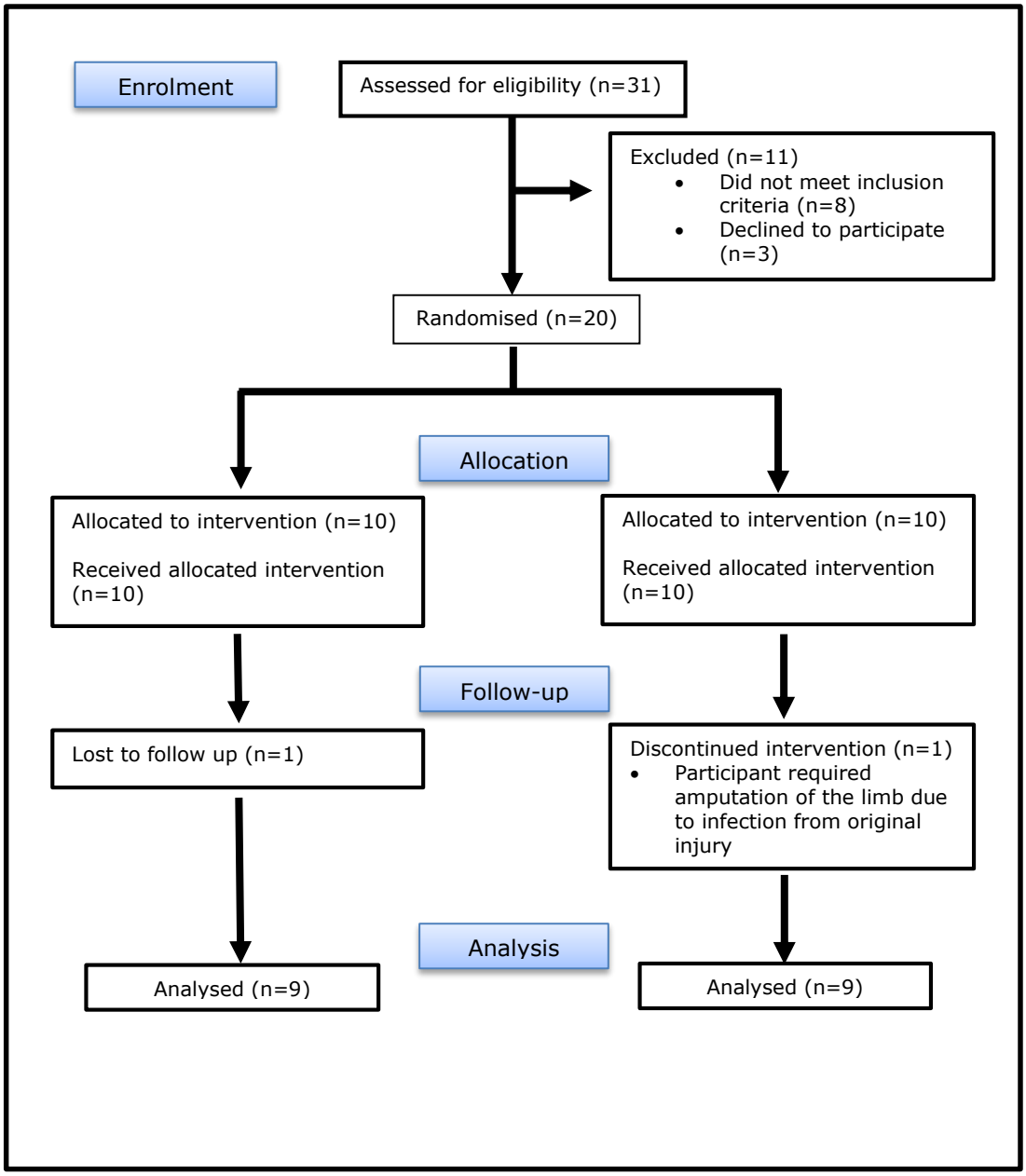
Participants

Between May 2013 and September 2014, thirty one patients were referred to the research team and assessed for eligibility for the study. Eight patients did not meet the inclusion criteria (Consent not obtained during designated recruitment period n=4, established osteomyelitis at the site for external fixation n=3, systemic infection n=1) and three declined to participate. Subsequently, twenty participants met the inclusion criteria and were randomised to either the antimicrobial collar group or standard care group. Follow-up was until the frame was removed, or until the study period ended (July 2015). Complications not related to infection were not analysed.

One participant from the antimicrobial collars group was lost to follow up. The second participant (standard care) discontinued treatment with external fixation due to aggressive osteomyelitis, which required amputation of the limb. The infection was acquired from the initial trauma (open injury). Pin sites were not reported to be infected at the time of amputation, although a sinus was reported in close proximity to one of the insertion sites. The frame was removed before the first follow-up appointment. These participants were not included in the data analysis as they did not meet the study requirements of follow-up data.

Participant outcomes were analysed according to the group they were assigned to at randomisation, rather than the final treatment they received. The Consort flow diagram is summarised in Figure 3.39.

Figure 3.39 Consort flow diagram for enrolment analysis



Participant demographics

Intervention and standard care treatment groups had comparable demographics with no statistically significant difference in age, number of participants with co-morbidities, or participants who smoked ($p>0.05$). Patient demographics are summarised in Table 3.16. No significant differences were detected between the groups regarding the number of elective frame applications, number of open or closed injuries, or the number of insertion sites for each group.

Only two female participants were included in data analysis, and both were allocated to standard care group.

Table 3.16 Participant demographics

	Standard care	**Active intervention**
Age *	41.78 ± 16.75	41.67 ± 17.66
Elective	3	2
Trauma		
• Closed fracture	1	3
• Open fracture	5	4
Mechanism of injury		
• Road traffic injury	2	2
• Fall	3	2
• Motor vehicle accident	1	1
• Industrial accident	1	0
• Assault	0	1
Number of pins *	3.89 ± 1.53	3.67 ± 1.73
Number of wires *	4.89 ± 2.84	6.44 ± 3.97
Number of insertion sites *	8.78 ± 2.28	10.11 ± 3.62
In employment	5	6
Occupation category		
• Unemployed	2	1
• Manager	0	2
• Professional	1	1
• Service and sales	0	1
• Agricultural	0	1
• Craft/trade	1	1
• Elementary	3	0
• Retired	2	2
Co-morbidities	3	3
Smokers	3	3

* Data presented as mean and standard deviation

Two participants from the standard care group were still being treated with external fixation when the study period ended. The final date of the study was taken as the end point for the purpose of data analysis. The treatment duration was recorded as 327 days and 555 days. All other participants completed their treatment regimen and had frames removed during the study period.

There were no significant differences between the antimicrobial and standard care groups regarding duration of treatment, or number of follow ups ($p>0.05$) there were no significant differences regarding the rate of PSI's, or the number of antibiotic courses prescribed or the severity of infection (Table 3.17).

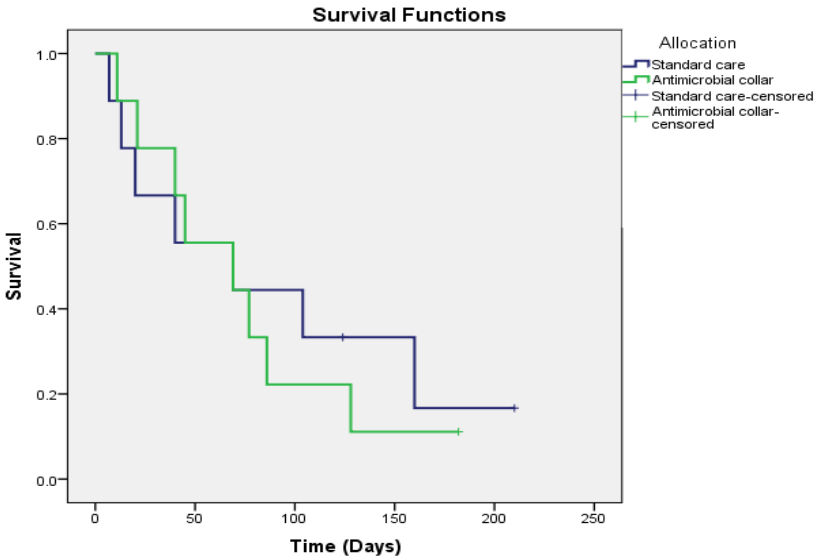
Table 3.17 Participant outcomes

	Standard care group (n=9)	**Antimicrobial collar (n=9)**	**p**
Number of patients with PSI	77.8% (n=7)	88.9% (n=8)	1.0
Duration of treatment *	226.11 ± 145.43	167.55 ± 63.35	0.28
Follow up appointments*	7.11 ± 4.34	5.44 ± 2.65	0.34
Number of recorded PSI*	3.89 ± 3.92	4.22 ± 2.95	0.84
Number of courses oral antibiotics*	3.00 ± 2.40	2.22 ± 1.99	0.46
Courses of IV antibiotics*	0.56 ± 1.33	0.11 ± 0.33	0.35
Severity of infection score*			
• Santy	5.00 ± 3.67	5.89 ± 3.72	0.62
• Checketts	1.44 ± 1.13	1.78 ± 1.20	0.55
• Patterson	6.90 ± 5.75	8.33 ± 4.85	0.57

*Data presented as mean and standard deviation

Kaplan-Meier survival analysis did not identify statistical significant differences for time till infection between standard care and antimicrobial collars (Figure 3.40).

Figure 3.40 Survival analysis – time till PSI



One patient from each group required intravenous antibiotic therapy for PSI, and further surgical intervention due to infection during the treatment period. For the participant from the antimicrobial collars group (CG), this additional treatment consisted of a short course of intravenous antibiotics and re-siting of a pin due to soft tissue infection. The standard care participant (RM) received four courses of intravenous antibiotics, three of which were lengthy courses delivered via the Outpatient Parenteral Antibiotic Therapy (OPAT) service to treat osteomyelitis, and five additional surgeries to re-site pins (due to PSI), debride the infected area, and insert antibiotic beads. As this participant initially sustained an open injury with extensive soft tissue damage, it is possible that infection may have occurred at the time of injury. This participant presented with PSI 20 days following frame application. During the study however it was noted on numerous occasions that the participant did not maintain a clean or aseptic approach to managing pin sites and used soiled dressings to wipe exudate from pins, or unwashed hands to remove crusts and exudate. Part way through the study it also became apparent that the participant took daily

baths and immersed the frame in the bath water for periods of up to an hour.

A participant from the standard care group (SH) was noted to have infection on removal of the external fixator, as identified from deep soft tissue samples from the pin track. The ensuing antibiotic management was not recorded and this occurred following frame removal.

Per protocol analysis

As five participants allocated to wear the antimicrobial collars did not adhere to the study protocol for the duration of the study a per-protocol analysis was performed. Reasons cited for removing the collars were forgetting to re-apply the collars after a shower, or when they had fallen off (n=2), the inconvenience of the collars falling off and losing them (n=1), local skin irritation caused by the collar (n=1), and collars being removed by the treating consultant following an episode of PSI (n=1).

There were no significant differences between groups analysed according to protocol adherence regarding age, number of participants who smoked or who had identified co-morbidities, number of insertion sites or duration of treatment (Table 3.18). No significant differences were identified between the number of patients with PSI, number of infected insertion sites, severity of infection or the number of antibiotic courses that were prescribed.

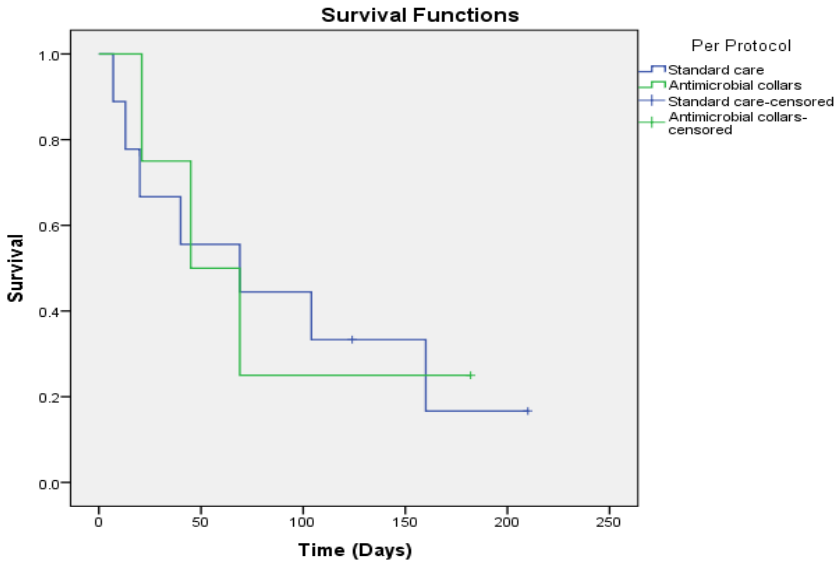
Table 3.18 Per protocol analysis of participant outcomes

	Standard care group (n=9)	**Antimicrobial collar (n=4)**	**p**
Age *	41.77 ± 16.75	43.25 ± 19.26	0.89
Number of pins *	4.33 ± 1.50	2.75 ± 1.50	0.11
Number of wires *	4.89 ± 2.84	9.50 ± 3.00	0.22
Number of insertion sites *	8.78 ± 2.28	12.25 ± 4.50	0.09
Number of patients with PSI	77.8% (n=7)	75% (n=3)	1.00
Duration of treatment*	226.11 ± 145.43	191.25 ± 81.93	0.67
Follow up appointments*	7.11 ± 4.34	7.00 ± 3.37	0.97
Number of recorded PSI*	3.89 ± 3.91	3.25 ± 2.50	0.77
Number of courses oral antibiotics*	3.00 ± 2.40	2.5 ± 3.11	0.76
Courses of IV antibiotics*	0.56 ± 1.33	0.25 ± 0.50	0.67
Severity of infection score*			
• Santy	5.00 ± 3.67	5.50 ± 4.20	0.83
• Checketts	1.44 ± 1.13	1.75 ± 1.26	0.67
• Patterson	6.90 ± 5.75	7.25 ± 4.35	0.91

*Data presented as mean and standard deviation

No significant differences were identified in the time till infection between groups using a per-protocol analysis (Figure 3.41). Of the participants who continued with the antimicrobial collar (n=4), one participant did not experience PSI (MS), one participant had a moderate infection and two were assessed as having a severe infection using the Patterson infection score.

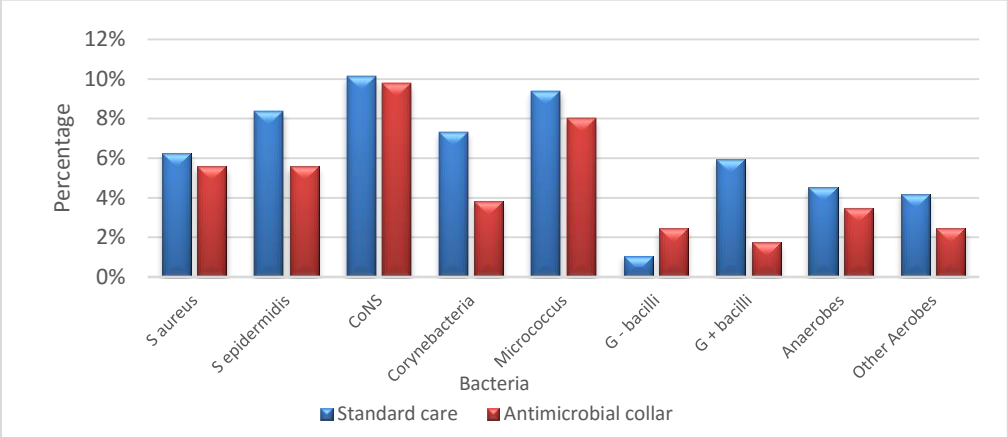
Figure 3.41 Per protocol survival analysis – time till PSI



Bacterial screen at three months

One–hundred and sixty swabs were obtained from participants' pin sites at three months. This equated to a mean 2.04 isolates per swab for standard care participants (range 0-7, median 2), and 1.51 isolates per swab for participants in the antimicrobial collar group (range 0-6, median 1), which was statistically significant (p=0.046) using a 2 tailed t-test. CoNS were the largest group of bacteria identified for both study groups (Figure 3.42).

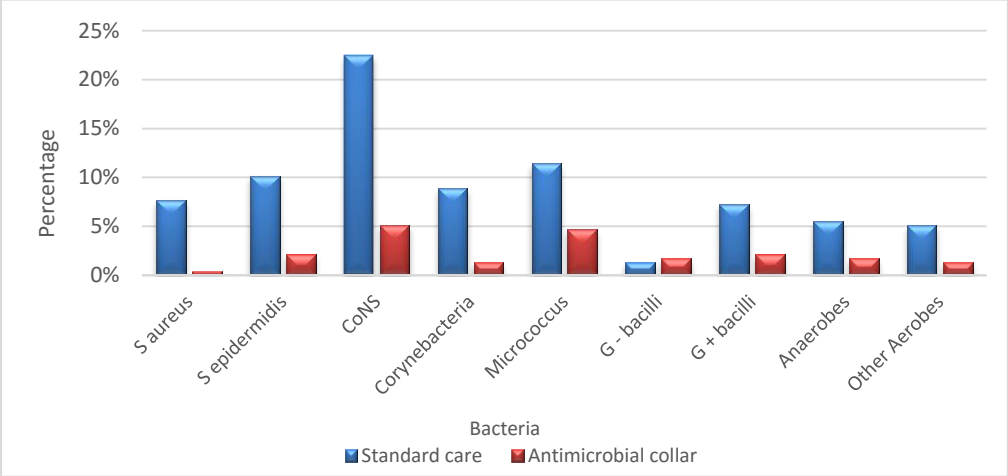
Figure 3.42 Bacterial isolates identified from participants at three months using assigned group allocation



MANOVA identified a statistically significant difference in bacteria isolated between standard care and antimicrobial collar ($F(10, 149) = 2.55$, $p=0.07$), although only gram positive bacilli were identified as statistically significant when assessing between subjects effects $F(1, 158) = 7.43$, $p= 0.007$.

Per protocol analysis of 3 month screening data identified a mean of 2.04 isolates per swab from standard care participants (range 0-7, median 2) and 0.98 from participants compliant with antimicrobial collars (range 0-6, median 0), which was statistically significant using a 2 tailed t-test ($p=0.01$). MANOVA also identified significant differences in bacteria identified between standard care and antimicrobial collar groups ($F(10, 113)=4.067$, $p<0.001$). Between subject analysis of bacteria identified significant differences with *S aureus* ($F(1,122) = 9.94$, $p=0.002$), CoNS (including *S epidermidis*) ($F(1,122)=6.78$, $p=0.01$) and corynebacteria ($F(1, 122) = 4.05$, $p=0.045$) (Figure 3.43).

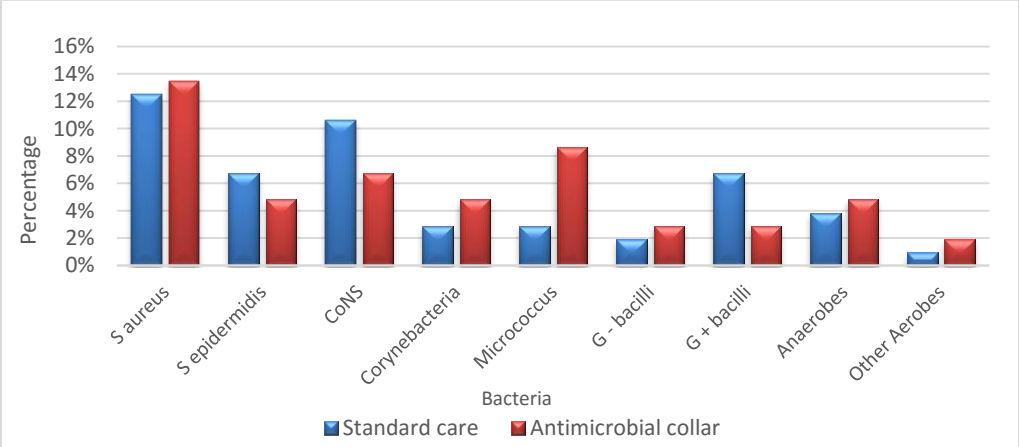
Figure 3.43 Bacterial isolates identified from participants at three months using per-protocol analysis



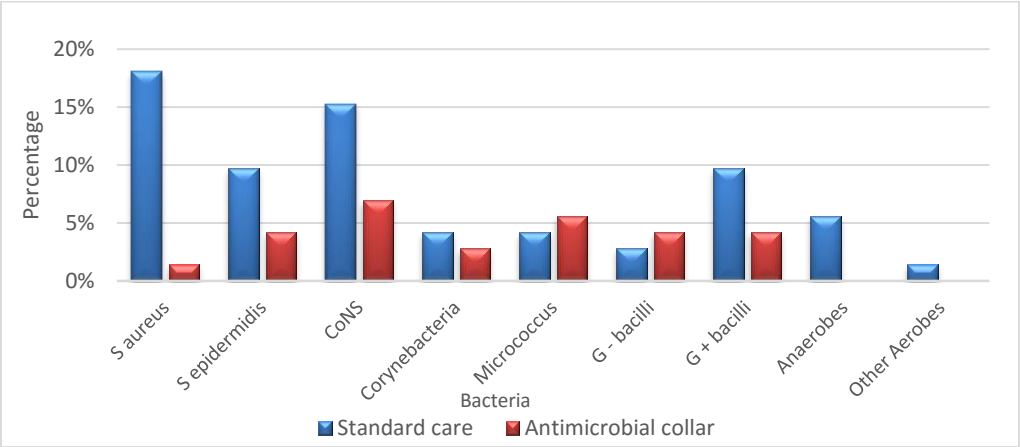
No statistically significant differences were identified between PSI bacteria between study groups using assigned group allocation (p=0.43) or per protocol analysis (p=0.14) (Figure 3.44). No statistically significant differences were identified between the infection score (Patterson score) and the number of bacterial isolates identified from PSI for group allocation or per-protocol analysis.

Figure 3.44 Bacteria isolated from PSI

a) Assigned group allocation



b) Per protocol



On calculating the percentage of PSI per frame standard care participants had a mean of 10.93% PSI (SD 10.71) and the antimicrobial collar group 13.57% (SD 13.44), which was not of statistical significance. Per protocol analysis identified antimicrobial collar participants had a mean of 5.5% PSI (SD 5.29), although this reduction was not of statistical significance.

Participant evaluation of collars

Completed questionnaires were received from six of the nine participants, giving a response rate of 66%. Of those who completed the evaluation form, only one respondent had a planned application external fixation, and all other applications were following trauma. Mean age of respondents was 43 years (median 37, range 22-71 years). All participants thought the collars were easy to apply, and the majority reported the collars to be comfortable to wear (83%, n=5) and easy to clean and use (83%, n=5). Some negative feedback was given regarding the collar remaining in place once applied as shown in Figure 3.45. Free text comments also revealed that the collars were prone to falling off once applied, and had a tendency to attract debris. Free text comments are summarized in Table 3.19.

Figure 3.45 Participant evaluation of antimicrobial collars

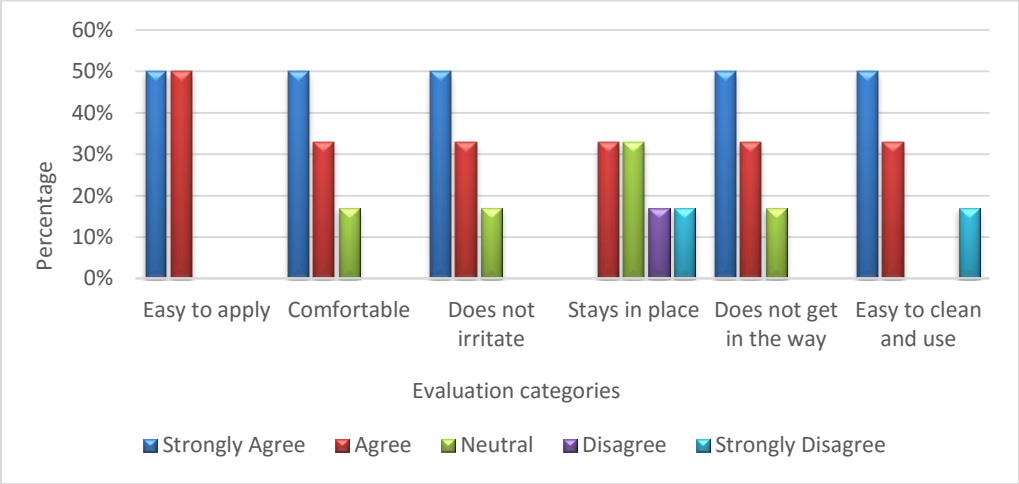


Figure 3.19 Participant evaluation of antimicrobial collars

Question lead	**Response and respondent number**
The collars are easy to apply	Fell off and collected dirt (3)
The collars are comfortable to wear	Itchy (3) Collected dirt under the collar (3)
The collars do not irritate the skin	Itchy (3)
The collars stay in place when applied	Two kept coming off in bed and occasionally when out and about (1) They fall off (3)
The collars do not get in the way of normal activities	I find the collars around the house (3)
The collars are easy to clean and use	-
Other comments	They picked up a lot of dust very quickly (1) They did not stay in place (2) The collars keep the pin sites very clean (4) The collars fall off the wires on the foot (4)

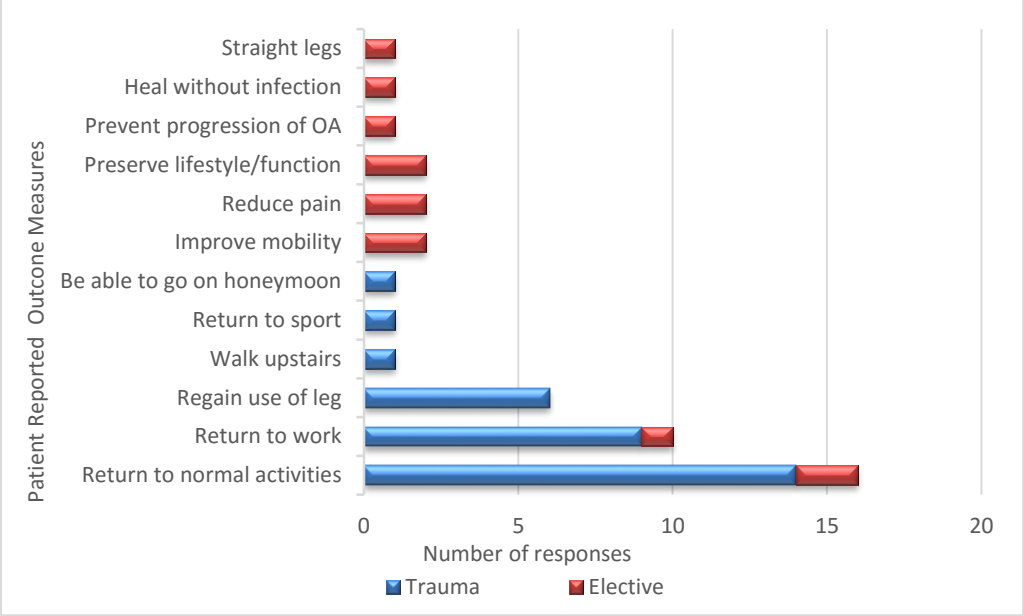
3.7 Patient evaluation

Patient reported outcome measures (PROMs)

Outcome measures were recorded from 26 patients before they were discharged from hospital after application of an external fixator, with the exception of one participant who was approached in the follow-up clinic. No patients approached regarding PROMs declined to participate. Six participants had frames applied electively for management of mal-union (n= 2), deformity (n=2), non-union (n=1) and infection (n=1). The remaining frames were applied for definitive management of complex fractures. Nineteen (73%) participants were male and all participants had external fixator devices applied to the tibia. Six participants (23%) were retired from active employment at the time of frame application.

Eighteen participants (69%) identified two desired outcomes, whereas eight (31%) specified one outcome measure. All elective cases identified two desired outcomes. Following thematic grouping of responses, a total 12 outcomes were identified. The most common outcome measures were the return to normal activities (61.5%), return to work (38.5%) and regaining the use of the leg (23.1%). Outcome measures are shown in Figure 3.46.

Figure 3.46 Patient reported outcome measures



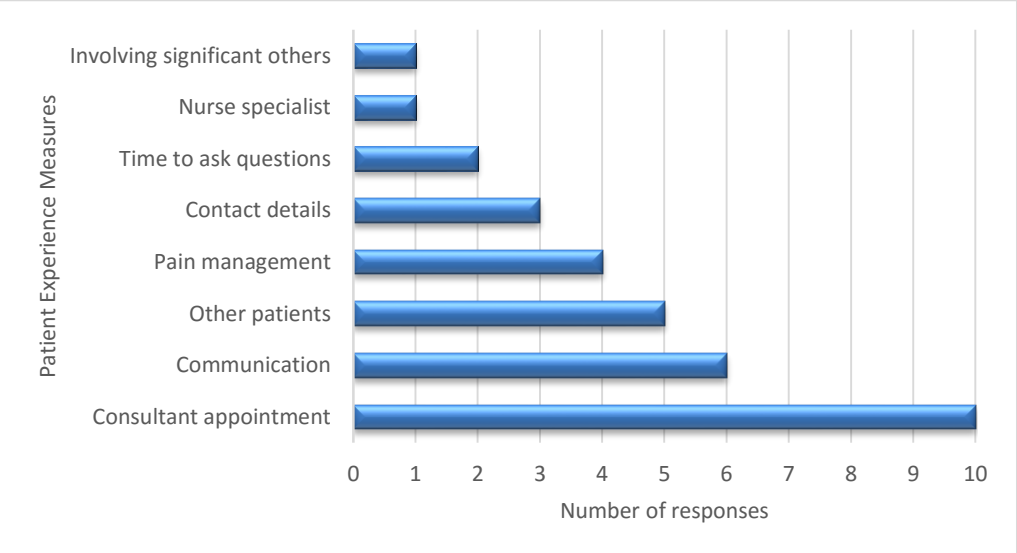
Overall 15 combinations of response were given. The leading combinations of responses from trauma patients included return to work and normal activities (30%, n=6), and regain the use of the leg and return to normal activities (20%, n=4). The most common single outcome specified by trauma participants was the return to normal activities (20%, n=4). Elective frame participants each provided a different combination of responses.

Patient reported experience measures (PREMs)

Sixteen adults with lower limb external fixation attending outpatient appointments were asked about experience measures. Experience measures were identified from 14 adults, two patients (one male, one female) stated that they were generally satisfied with care and were unable to identify key areas of experience which they felt could be used as future experience measures. Of those who participated, eleven respondents (78.6%) had frames applied following trauma, three (21.4%) were retired from employment, and two (14.3%) were female.

Twenty eight responses were recorded from the fourteen participants. Following thematic grouping of comments, eight distinct experience measures were identified (Figure 3.47). Communication factors were the most common aspects viewed as being central to the frame experience. This included communication between the hospital and the patient, community team and the multidisciplinary team (42.9%, n=6), seeing the consultant at follow-up appointments (71.4%, n=10), having sufficient time to discuss care and ask questions of the consultant (14.3%, n=2) and knowing whom to contact with concerns between appointments (21.4%, n=3). Reasons specified for seeing the consultant at follow up appointments predominately focused on inconsistences with other members of the team not knowing the patient/management plan/ongoing issues, and members of the team being unable to make decisions regarding frame management. Remarkably only one patient thought seeing the nurse specialist was a key experience measure.

Figure 3.47 Patient experience measures



Peer support was highlighted as being an important part of patient experience by 35.7% (n=5), specifically highlighting the help and support gained from seeing other people with external fixator devices in clinic. One patient commented "the opportunity to share experiences helped me to cope with the frame experience – knowing I am not alone". This was also echoed by others who highlighted the benefit of comparing frames, experiences, hints and tips with other frame patients in clinic.

Chapter 4 Discussion

4.1 Survey of current pin site care regimens

The use of an electronic questionnaire permits access to a large number of people over a large geographical region, and facilitates easier sampling than methods such as telephone interviews or observation of practice. The absence of the 'interviewer effect' (Parahoo 2006) with an on-line anonymous questionnaire allows participants to respond openly without concern that clinical practice can be questioned by the researcher. The disadvantage of the questionnaire however, is that response rates may be lower and points cannot be clarified either by the researcher or the responder (Parahoo 2006).

While it is acknowledged that surveys often have low response rates, the current response rate of 23.7% is less than the average 33% for on-line questionnaires or 56% for paper questionnaires (Nulty 2008). The UK response rate was higher than the overall response rate and reflects the anticipated response rate for on-line questionnaires. As the survey was anonymous it was not possible to identify who had replied, and therefore repeat email reminders were not sent out to remind non-responders. A generic email sent to all potential participants reminding non-responders to compete the survey, may have increased the overall response rate.

The survey sampled those working within the speciality of external fixation. However, it is not possible to claim that the sample is representative of practitioners across the UK, or internationally due to the small sample size, and methods used to identify potential participants. Respondents were not asked if they were aware of the UK Consensus guidelines as this may have influenced responses given, although this would have provided valuable

insight as to whether practitioners were not aware of the guidance or non-compliant with the recommendations.

Santy and Newton-Triggs (2006) conducted a similar scoping exercise of orthopaedic and trauma nurses. Details were not included regarding response rates although 144 questionnaires were included for analysis. Demographics included 74.4% UK respondents, and 19.4% unidentified respondents. Although similarities can be drawn between Santy and Newton-Triggs' (2006) survey and the current study, statistical significance cannot be ascertained as the current study aimed to evaluate current practice rather than replicating the previous survey.

Cleansing pin sites

Of the responses analysed 47.9% (n=34) UK nurses and 38.2% (n=71) of UK practitioners used alcoholic chlorhexidine compared to 18.1% (n=23) international practitioners. It is of interest to note that 33.8% (n=25) of UK nurses specified using normal saline or water (6.8%, n=5) to clean pin sites when UK consensus guidelines recommend alcoholic chlorhexidine solution (Timms et al 2011). This may in part be due to high levels of hypersensitivity (17.6%) associated with the use of alcoholic chlorhexidine as reported by Davis et al (2005), or due to the lack of adequately powered studies evaluating different cleansing solutions relative to PSI (Lethaby et al 2013) and side effects experienced.

Santy and Newton-Triggs' (2006) previous survey reported that 74.6% practitioners cleansed pins using normal saline. This suggests that cleansing practices have changed since the publication of Timms et al's (2011) consensus document, although recommendations have not yet been universally accepted as routine practice within the UK or internationally.

Frequency of care

The majority group of clinicians cleansed pin sites once daily with 37.4% (n=120) in comparison to 20.6% (n=66) weekly. Daily cleansing was preferred by both international and UK practitioners with (41.9%, n=55 and 33.7%, n=64) compared to weekly (12.2%, n=16 and 27.9%, n=53). Timms et al (2011) and Lethaby et al (2013) both highlight the insufficient evidence to guide frequency of care, suggesting further research is required. Conflicting results in the literature suggest no significant differences in PSI between weekly and daily pin site care (W-Dahl 2003), or between no cleansing and daily irrigation with saline (Camathias 2012). Interestingly Kao et al (2014) report significantly higher PSI rates with daily cleansing with 75% alcohol compared to no cleansing ($p=0.007$).

Santy and Newton-Triggs' (2006) reported that 61.8% practitioners cleansed pins daily. Weekly cleansing was not represented in the results, indicating this was not common practice. Santy and Newton-Triggs (2006) also reported fewer than 10% cleansed pins every 3 days, and < 5% cleansed alternate days, indicating a gradual change in practice.

It is of interest to note that 6.5% (n=21) practitioners in the current survey do not clean pin sites. This question may have been misinterpreted by some respondents selecting "do not clean pin sites" meaning they do not personally clean pin sites, rather than the care they advise, however clarification of responses were not possible due to the anonymous nature of the questionnaire. Santy and Newton-Triggs (2006) also reported a small number of practitioners (1.4%) did not cleanse pins using a solution.

Crusts

Removal of dried crusts/exudate was advocated by 57.9% (n=186) respondents (55.8% n=106 UK practitioners). While this represents the majority answer, this is less unanimous than previously reported by Santy and Newton-Triggs (2006) (89.6%), again signifying a gradual change in practices. Britten et al (2013) suggests that retention of adherent crusts protect against the developing PSI, although cause infected pin sites to become more refractory to treatment. No further studies investigating the role of pin site crusts have been identified, and therefore warrants further evaluation.

Dressings

The use of dressings can be divided in to two categories: those which are used during the initial post-operative period when bleeding and serous drainage may be evident, and those which are used once the drainage has stopped. This difference was not addressed in the current survey, although would have offered a more detailed review of the dressings used. The current survey identified 50.3% (n=160) practitioners (51.9% n=68 UK practitioners) left pin sites exposed, even though present guidelines (Timms et al 2011) recommend pin sites should remain covered. This response is relatively unchanged from the 51.4% practitioners reported by Santy and Newton-Triggs (2006) who continued to dress pin sites after the initial post-operative days. There are currently no trials which have compared PSI relative to dressed or exposed pin sites (Lethaby et al 2013). Clear comparison of infection rates and complications would help align clinical practice in this area. The heterogeneous nature of existing studies and methodological shortfalls again fail to guide clinical practice, as evidenced in the diverse approach to dressing use in pin site management.

Overall 13.5% (n=43) used dry gauze to dress pin sites, with an increased prevalence in international responses (19.8% n=26), compared to 9.1% (n=17) UK practitioners and by the medical team 17.0% (n=31) compared to 11.6% (n=14) of nurses. This may be attributable to an increased awareness of alternative dressings by nurses, limited availability of some dressings internationally, or simply the frequent availability and relatively low cost of gauze.

Chlorhexidine-soaked gauze was used to dress pins by 12.9% (n=41) practitioners and favoured more internationally (29.0% n=9), than in the UK (17.1% n=32). The use of chlorhexidine-soaked gauze was previously reported to be used by fewer than 5% practitioners by Santy and Newton-Triggs (2006), suggesting a relatively new development in pin site practices which has gained a gradual increase in popularity over recent years. Similarly foam dressings did not feature in Santy and Newton-Triggs (2006) survey although they were reported by current practitioners. The use of film dressings such as Tegaderm (3M) or Opsite (Smith-Nephew) were not reported as common dressings within the survey or by Timms et al (2011), although were previously used by 11.1% as reported by Santy and Newton-Triggs (2006).

The increasing number of trials investigating the effects of different dressings on PSI (Grant 2005; Patterson 2005; Camilo 2005; Egol 2006; Yuenyongviwat 2011; Camathias 2012; Lee 2012, Ogbemudia et al 2015), are encouraging, although small study populations and heterogeneous designs make comparison of data challenging. Current results highlight a clear lack of consensus regarding dressing of pin sites.

Compression of pin sites

Movement at the skin/pin interface can contribute to irritation and discomfort, although scanty research specifically compares the effects of dressings on the movement at the pin/skin interface. Studies by Paley and Jackson (1985), Schweinberger and Roukis (2008) and Dayton et al (2011) describe the use of compression at pin sites, although little evidence is available to demonstrate the effectiveness of compression in preventing discomfort, haematomas or infection, or to substantiate proposed methods, extent of compression or complications that may occur as a result of continued pressure over prolonged periods.

In the current survey compression was applied by 46.8% (n=88) UK practitioners. Compression was referred to by Santy and Newton-Triggs (2006) although responses were not formally reported. Equally compression at the pin sites did not feature in the previous UK consensus guidelines (Lee-Smith et al 2001), indicating that this is an evolving practice which requires further research.

Bathing and showering

Lethaby et al's (2013) Cochrane review pooled data from studies by Cavusoglu (2009) and Patterson (2005) comparing sterile cleansing techniques with non-sterile cleansing techniques (soap and water/showering), and reported no significant difference between infection rates. While bathing was generally not encouraged (73.2% n=219 advising against bathing), showering was permitted by the majority of practitioners (82.0% n=242). This area of practice remains largely unchanged as Santy and Newton-Triggs (2006) similarly reported that 78.5% practitioners allowed patients to shower and also reflects current UK consensus

guidelines (Timms et al 2011) of allowing patients to shower, but not bathe while external fixation remains in place.

Limitations and further work

Limitations of this survey include the poor response rate of 23.7% and singular responses from many countries, which reduces the reliability and generalisability of the findings. The strengths of this survey include a larger number of responses than the previous study by Santy and Newton-Triggs (2006). Questions of the current study reflect areas of practice outlined by the UK national consensus guidelines (2012) and therefore offer an insight to current practices and changes that may have occurred in the UK in response to the guidance. As previous published work has not explored pin site care internationally comparisons over time cannot be made with the current findings. This survey also considered differences between professions and geographical location with regard to pin site practices, which has not yet been explored.

This study has clearly identified inconsistencies in pin site care both in the UK and internationally. Research available on pin site management is often retrospective cohorts which lack randomisation or control groups, based on small study sizes, or of poor methodology. It is possible therefore that inconsistencies in practices are attributable to the poor evidence underpinning clinical practices. Further research is required to determine if routine cleansing of pin sites reduces PSI and to establish which skin cleansing routines (if any) provide effective clearance of bacterial colonisation at the pin site, and the optimal frequency that this should occur to prevent PSI. Ideally this should include a range of control (no cleansing or normal saline) and antimicrobial solutions. Similarly, the use of dressings need to be carefully evaluated with regard to if they are

effective in preventing PSI, and which dressings are most effective in doing so. This would preferably include a variety of dressings identified from the survey, such as dry gauze, soaked gauze, dressings with sealed edges, such as Allevyn, and dressings marketed as having antimicrobial properties, such as Biopatch. Similarly the role of compression in preventing pin site care requires prospective analysis considering the force applied, methods in which it is applied, and complications associated with this in relative to PSI prevention.

Summary

The current survey highlights the diversity of practice when caring for pin sites, both between professional groups, and internationally. The current survey demonstrates some consistency regarding frequency of care, crust management, use of dressings and compression although does not identify unanimous practice in any of the areas surveyed. Relatively few areas of UK practice align to Timms et al's (2011) UK consensus guidelines, particularly the use of compression, dressings and frequency of care. Potential reasons for this include practitioners not being aware of the guidelines, or non-acceptance of the guidelines due to the lack of high quality evidence on which the guidelines are based.

Some practices have evolved over recent years when comparing results from the current survey to Santy and Newton-Triggs' (2006) previous findings. Well designed, adequately powered studies are still required to investigate the cause-effect relationship of pin site care to infection to determine best practice. Based on the findings of this survey, it seems that a novel antimicrobial disc may contribute to the care of pin sites and reduce PSI. Similar products were not identified within the survey.

4.2 Pin site assessment criteria

Clinical assessment tools provide a mechanism for scoring and ensuring a consistency of data collection. An ideal tool is quantifiable, valid, and sensitive enough to allow a range of values across the spectrum, while being responsive to changes (Singh et al 2015). It should also be easy to perform with high inter- and intra-observer reliability to ensure consistent use in clinical practice.

Inter-observer reliability was used to determine the degree of observer agreement between scores. Despite the objective nature of the Patterson tool there was low inter-observer agreement for this criterion (ICC 0.621). Intra-class correlation of 0.7 or higher typically indicates adequate agreement in scoring between independent observers (Walker et al 2011). This suggests that both Checketts and Santy tools offer more consistent rating between observers.

While the average measures scores were substantially higher than single measures for all tools, single measures are more appropriate to the clinical context as typically only one clinician will review pin sites during consultation, rather than an average of scores being reported. Again as agreement between the observers is of more interest than consistency, absolute agreement was selected to determine the reliability of overall scores.

Two-way repeated measures ANOVA identified significant differences between observers and time for the Checketts tool ($p=0.01$), although not for Patterson ($p=0.4$) or Santy ($p=0.05$). This is reflected in the ICC for the test and retest scores when using only data available for both test and retest assessment, with Checketts scoring 0.671 and 0.828, Patterson

scoring 0.569 and 0.636, and Santy scoring 0.866 and 0.856 respectively. While ICC remains low for the Patterson score at test and retest, there is no significant difference between the two assessments. This may be due to lack of specific training on the tool prior to use, and although observers were consistent with their own scoring this did not correlate to scores of other observers. As observers were asked to score pictures of pin sites, this may also have impacted upon the ability to determine factors such as erythema and to quantify objectively, for example, >2cm diameter, as pictures did not include a scale.

Of particular interest is the difference between the ICC measures for all observers using the Checketts tool (ICC 0.814) compared to those who completed both components (0.671 and 0.828). Although all original participants were asked to complete both stages, lack of time and a busy clinical workload were cited by participants as being the main reason that they did not complete the second stage. Singh et al (2015) state that more complex tools increase the risk of non-completion or inaccurate assessments, which might also explain why several participants did not complete the second stage. Differences in scores may have occurred due to an increased familiarity with the tool at the second assessment. However, this was not as evident with the other tools. Significant differences between inter and intra observer reliability may therefore impact upon the clinical effectiveness of the tool.

As pin sites are chronic wounds it is important to consider the signs of acute and chronic infection as part of the assessment criteria (Cutting and Harding, 1991, Gardner et al, 2001). All scales were acceptable to the clinicians, although the straight-forward nature of the Santy tool, which linked directly to patient experience, was noted as a positive aspect. The Patterson tool also received positive feedback due to the objective scoring

nature. Singh et al (2015) suggest that an effective tool should ideally differentiate between severity of disease. Although this is not a component of the current Santy tool, this does not appear to detract from the usefulness of the tool in identifying infection. Despite the lack of quantification of infection severity the Santy tool demonstrated high ICC at both test and re-test stages and no significant interaction between observers and time therefore making the Santy tool the most reliable. This would need to be tested with other health disciplines to confirm its generalisability across practice and using actual patient pin sites rather than pictures.

Limitations of this design include the use of a small sample of observers from one NHS Trust, all of which were experienced nurses working in orthopaedic trauma. Other limitations include the use of pictures of pin sites. Clinical assessment using touch, colour and smell requires subjective judgement (Gardner et al 2001), and therefore the lack of personal interaction may have affected the subjective patient assessment, or clinical impression regarding the state of the pin site. However, the use of pictures served to reduce potential sources of variation between observers and time points to facilitate a constant outcome, which is an essential component of the test-re-test principle (Lee et al 2011).

The current review does not assess the validity of the signs and symptoms associated with PSI, or the sensitivity of each criterion in identifying infection. However this was previously described by Patterson (2005) and the criteria of Santy et al (2011) were derived from patient experience and therefore likely to have high levels of content validity.

Further testing of the tools may include community assessment, other health professional groups and patient assessment to compare differences between grading. It would also be of interest to evaluate the effects of specific training sessions on PSI and use of grading tools to determine if this would improve reliability. As the tools each require an element of clinical judgement, it would also be useful to consider results in relation to clinical experience of the observers.

Using the data from the initial tests, power calculations can determine the ideal numbers of observers and number of pin sites to evaluate. Gwent (2014) suggested that a larger number of subjects increases the inter-observer reliability coefficient, but, consideration is also required to determine the appropriate number of observers required to improve the precision of the intra-observer reliability.

Summary

Clinical tools are an important part of patient assessment and it is vital that they are easy to perform in a short time frame and ideally do not require specific training.

In conclusion PSI tools provide reproducible and reliable methods of assessing PSI. The tool developed by Santy et al (2011) demonstrates high inter and intra-observer reliability indicating that this tool offers a more consistent and reliable approach to assessing for PSI, when compared to the Checketts tool which demonstrated variable inter-observer reliability and significant differences for intra-observer reliability, and the Patterson tool which revealed lower consistency scores between observers, although no significant differences with intra-observer assessment.

4.3 Evaluation of bacteria

Characteristic microbial environments exist due to indigenous site specific factors, such as areas of skin densely populated with sebaceous glands (Grice et al 2009). Changes to conditions may result in dysregulation of environmental constraints and subsequent changes to the composition of bacteria (Oh et al 2013). As there is a paucity of data which focuses on the bacteria present from non-infected pin sites, comparisons between patient populations, health care settings or pin site management cannot easily be drawn from the current data. A greater diversity of isolates as well as a higher number of species per swab were identified from non-infected samples. The lower number of species identified from PSI samples suggests that the increased bacterial load at infected pin sites dominates other skin flora, reducing the number of other bacterial isolates identified per swab.

There were no significant differences between site of insertion for tibial pins and wires, which contrasts with reports from Treadwell (2005) and Schalamon et al (2007). Statistical analysis of foot and femoral samples were not completed due to small numbers, but this would provide a broader context to the current findings. The current evaluation did not initially seek to identify the prevalence of infection in pins or wires and therefore the design of the evaluation may have led to coincidental findings.

The higher number of bacteria identified from wire insertion site infections may be associated with local factors such as movement around the skin pin interface (Inan et al 2004), the thickness of soft tissue (Moroni et al 2002a), ease in which patients may clean around wires if they are in close proximity of each other, or if entry sites are not easily viewed or reached.

Further work is therefore required to systematically identify the prevalence of infection and bacteria identified from pins and wires and potential variables which may contribute to the differences observed.

Large numbers of staphylococcal isolates were isolated from both healthy and infected sites. It was anticipated that *S aureus* would be identified as part of skin flora, as approximately 20% of people are persistent carriers in the anterior nares and, 60% intermittent carriers (Kluytmans et al 1997). *S aureus* notably has many virulence factors including adhesins, and is a dominant pathogen for both superficial infection and osteomyelitis (Lory 2014, Zecconi and Scali 2013, Ribeiro et al 2012). While it is challenging to distinguish between true pathogens and skin flora, the significantly higher isolation rate of *S aureus* in PSI strongly suggests that *S aureus* is a causative factor for PSI.

Despite no significant differences between the number of CoNS in PSI and non-PSI samples, CoNS are often implicated in infection. Interestingly *S lugdunensis*, noted for its pathogenic potential and association with skin, soft tissue and implant infections (Kleiner et al 2010, Zinkernagel et al 2008) decreased from 3% of non-PSI isolates to <0.5% in PSI ($p < 0.05$).

Corynebacteria were more prevalent (10.7%) at clinically non-infected sites compared to PSI (6.6%) although this was not statistically significant. Corynebacteria are known to cause osteomyelitis and implant infection, with *C jeikeium* being the most common corynebacteria identified in orthopaedic infection (Rizvi et al 2011). The presence of coryneforms in PSI therefore should not be overlooked due to their pathogenic potential and multidrug resistance (Bernard 2012, Harrington et al 2014).

P acnes is also a major colonizer of the skin and has been associated with soft tissue and implant infections (Achermann et al 2014). Again, no

significant differences were identified between infected and non-infected sites, though, as propionibacteria are known to predominate where there are an abundance of sebaceous glands, such as the face and upper body (Grice et al 2009), it is anticipated that there would be an increased prevalence in isolates obtained from halo or upper limb pin sites, particularly above the elbow.

Orthopaedic infections due to *Clostridium* spp are not frequently reported. However they are associated with severe deep infection that is challenging to treat (Ibnoulkhatib et al 2012). Comparable prevalences of Clostridium were identified in both infected and non-infected pin sites. While necrotising clostridial infections such as *C perfringens* and *C Sordelli* can be rapidly progressive, this consequence was not observed in any of the patients in which they were identified. This may be due to insufficient factors required to expedite infection, such as the degree of tissue hypoxia (Stevens et al 2011).

C difficile has not previously been noted to be a common pathogen for skin or pin sites, although it was identified from both infected and non-infected pin sites. The ease in which *C difficile* can be transmitted to other sites from skin contamination has been highlighted by Bobulsky et al (2007) as a potential source of *C difficile* infection. This is particularly important given the multiple antibiotic courses often required by patients with external fixators. Asymptomatic carriage is not routinely screened for with this patient group, even though carriage may contribute to transmission (Donskey 2010). Although it is not practical to screen routinely for carriage, it may be a worthwhile consideration to include this as part of a pre-operative screening as with MRSA screening, or when PSI is suspected.

In assessing patients with PSI Antoci et al (2008) and Marsh et al (1997) calculated the number of patients with organisms rather than per swab or site. Although this diminishes the effect of cross contamination between pins and potential duplication of isolates, it does not allow discrimination between healthy and infected pin sites. The current evaluation identified 55% (n=16) PSI patients with *S aureus*, 48% (n=14) with *S epidermidis* (76% CoNS overall, n=22), 38% (n=11) with corynebacteria, 31% (n=9) with *P acnes*, 24% (n=7) with gram negative bacilli, and 10% (n=3) with *clostridium* spp. Antoci et al (2008) also reported large numbers of patients with *S aureus* (47%), although only 12% with *S epidermidis*. In contrast to the current findings Antoci et al (2008) reported higher numbers of *E coli* (9%) and streptococcal infection (4%). Marsh et al (1997) also reported a large proportion of patients with *S aureu*s (41%), and *S epidermidis (*32%), similar numbers of pseudomonas, and again higher numbers of coliforms (9%) than in the current evaluation. The results maintain similar rank orders, although show inconsistencies potentially due to numbers of patients sampled, number of swabs taken from each patient, patient demographics, pin site care, or other variables such as previous infection, the use of antibiotics or the length of time the frame has been in-situ.

Antimicrobial sensitivity

The aim of the antimicrobial collar is to prevent colonisation of the pin site and subsequent infection. The combined antimicrobial agents (clindamycin, rifampicin and triclosan) are designed to reduce the risk of resistance in accordance with the dual drug principle (Zhao and Drlica 2001). They also offer broader coverage with combined use and potential synergy of the antimicrobials (Tamma et al 2012). As only 4.5% (n=1) of the anaerobic bacteria tested were resistant to the collar antimicrobials, it is also

anticipated that the collar would provide effective protection against these bacteria. Due to innate bacterial resistance the antimicrobial collar will not provide antimicrobial coverage for *Enterococcus*, *Pseudomonas* and *Acinetobacter* species, although these only accounted for 1.56% isolates identified from infected pin sites.

Gram-positive cocci were the most common group of isolates identified within the evaluation, and those tested demonstrated high sensitivity levels for the selected antimicrobials with 91% of *S aureus* and 97% of CoNS being sensitive for two or more of the antimicrobials. This was reduced for micrococci at 70%. Although micrococcus is frequently described as an opportunistic pathogen (Oudiz et al 2004), it is rarely thought to cause infection in non-immunocompromised individuals (Gohel et al 2014). Despite the reduction in micrococci sensitive to two or more of the selected antimicrobials, none of the micrococci were resistant to all three. It is therefore expected that the collar will prevent micrococcal colonisation of the pin site, along with colonisation by other gram positive cocci.

A small number of corynebacteria isolated (6.7%, n=1) were found to have resistance to all three drugs in the collar. This was not unexpected due to the multidrug resistance often identified with corynebacteria (Bernard 2012). As triclosan offers broad spectrum antimicrobial activity against gram positive and gram negative bacteria it is anticipated that this component will provide protection against gram negative bacilli which is not provided by clindamycin or rifampicin. However, *Pseudomonas* has been reported to be highly resistant to triclosan (Russell 2004) and decreased susceptibility in *E coli* due to efflux pumps (Suller and Russell 2000).

Of the isolates tested for sensitivity against the antimicrobials used in the collar, only 3.85% were resistant to all three. As the majority of isolates tested were sensitive to at least one of the antimicrobials used this suggests that the antimicrobial collar will successfully reduce bacterial colonisation of the pin site, and subsequent infection. The antimicrobial activity of the collar could potentially be increased by adding an additional antimicrobial, such as sparfloxacin or trimethoprim, or using different combinations of antimicrobials, as has been done with antimicrobial catheters (Bayston et al 2009, Fisher et al 2015). Each antimicrobial combination would need to be compatible, heat-stable to allow for autoclaving and be able to migrate across the polymer. Antimicrobials also need to be soluble in chloroform for successful impregnation.

Biofilm formation

Biofilm formation is an important virulence factor. From the isolates tested, each of the bacterial categories demonstrated ability to form biofilms, with 60% of isolates tested producing moderate or strong biofilms. However, as only 24 gram positive bacilli and three gram negative bacilli were tested, additional testing would more adequately demonstrate patterns of biofilm formation in these groups.

The ability to form biofilms partly explains why normal flora traditionally considered non-pathogenic may become pathogens in the presence of foreign bodies (Tande and Patel 2014). This is of particular relevance due to the low number of micro-organisms necessary to establish an infection in the presence of an implant (Elek and Conen 1957). The most common organisms identified from biofilm-infected devices are *S aureus* and CoNS (Vickery et al 2013), which corresponds with the bacterial evaluation

findings which identified CoNS and *S aureus* as the most prevalent isolates from clinically infected pin sites at 33.2% and 17.9% respectively.

The current biofilm quantification method sought only to investigate single strains for biofilm infection. Biofilms may be polymicrobial in-vivo and consist of different sub-populations with different phenotypic or genotypic characteristics (Tande and Patel 2014), which may produce different outcomes from those observed in-vitro. Factors such as bacterial adherence and environmental factors can affect biofilm formation (Donlan 2001). Site of insertion and implant material (Ramage et al 2003; Qi et al 2008), therefore require further consideration before clinical interpretation of the current results.

Due to the nature of biofilms, and strong adherence to the biomaterials, it is possible that bacteria from established biofilms were not identified using the swab sampling of superficial sites in the initial evaluation. This may have led to an underrepresentation of the number of strong biofilm producing bacteria present at pin sites. It would therefore have been useful to examine pins and wires after removal for evidence of biofilms and contrast results between clinically infected and non-infected samples. Due to the increased tendency for biofilms to develop the longer the device remains in-situ (Donlan 2001), it would also be of interest to consider time as an additional variable.

Biofilm formation makes eradication of the bacteria difficult due to the increased resistance to host defences and antibiotics compared to the planktonic form (Prabhakara et al 2011). Preventing contamination of implantable devices is the ultimate goal, but with the ubiquitous nature of common infecting organisms this is challenging (Vickery et al 2013). The antimicrobial collar aims to prevent colonisation of the pin site, thus

preventing subsequent biofilm formation and infection. As the bacteria identified in the evaluation were predominantly sensitive to the antimicrobials used within the collar, it is expected that the collar will prevent biofilm formation in the clinical setting.

Limitations

Limitations of this evaluation include the small number of swabs from femoral sites, and from the foot. Greater numbers of samples from these sites would increase the generalisability of the findings. Due to the topographical variation between sebaceous, dry and moist environments (Oh et al 2013), samples from other sites such as halo pins or upper limb sites would provide greater insight in to PSI pathogens. The strength of this study is that all samples are obtained from lower limbs; increasing the reliability of findings.

Further work

Pathogens are often considered as discrete variables in virulence studies, but the complex relationship between the patient, overall health and activity of the patient needs to be considered as factors that may change pin site microbiology. It would therefore be valuable to note the effect of co-morbidities and/or the use of regular medication on pin site isolates, as with pathologies relating to the skin such as psoriasis or dermatitis. Further areas to consider include depth of soft tissue, objective degree of movement at the skin/pin interface, and if the frame is undergoing adjustments. It would also be of interest to consider the length of time the frame has been in situ, and severity of infection in relation to the isolates identified.

Summary

It remains a challenging task to determine the significance of positive cultures and distinguish between skin flora and pathogens. While many of the bacteria identified are present as skin commensals at 'healthy' pin sites (as identified in the bacterial evaluation), opportunistic entry at the pin site may lead to infection. All isolates therefore could be considered as potential pathogens.

Understanding the variation of bacteria identified in PSI and non-PSI states increases understanding of potential infective sources facilitating appropriate preventative strategies. From the current evaluation, there was a significant increase in *S aureus* in PSI when compared to 'healthy' pin sites, and this organism therefore may be considered an expected pathogen in PSI.

Based on the bacteria identified in the evaluation and subsequent sensitivity testing the combination of clindamycin, rifampicin and triclosan in the antimicrobial collar is expected to be effective in reducing PSI, and subsequent biofilms in clinical conditions.

4.4 In-Vitro testing

SPTT

Testing of individual drugs identified clear zones for 100 days with triclosan, when the SPTT was stopped, but zone sizes for clindamycin and rifampicin rapidly declined and failed at Day eleven and Day sixteen respectively. Impregnation and SPTT were repeated for F2903 (*S aureus*)/clindamycin to confirm results. These findings were consistent with earlier work by Bayston et al (1989) which tested individual impregnations of clindamycin and rifampicin under flow conditions testing hydrocephalus shunts.

As zone sizes were consistently and significantly larger for combined antimicrobial discs tested with F2903, this suggests that the antimicrobial combination may be synergistic, where the combination is greater than the sum of the drugs independently (Acar 2000). The lack of significant difference in ZoI with F1693 between single drug and combined antimicrobial impregnation reflects the known resistance of the strain to clindamycin and rifampicin.

Previous testing of peritoneal catheters impregnated with rifampicin, trimethoprim and triclosan has demonstrated antimicrobial activity for over 270 days against *S aureus* and *E coli* (Bayston et al 2009), which supports current results and longevity of antimicrobial action of the antimicrobial collar impregnated with clindamycin, rifampicin and triclosan. The antimicrobial disc successfully maintained large ZoI for over 90 days against test isolates (*E coli*, *S aureus*, CoNS and *corynebacteria*) selected to reflect potential PSI pathogens. The antimicrobial collar failed to create a ZoI at Day 15 (F3501) and Day 48 (F3412) for two corynebacteria

strains. As strain F3501 was sensitive only to rifampicin within the collar, these results are consistent with the earlier individual impregnation results. Strain F3412 was sensitive to both clindamycin and rifampicin, again suggesting synergistic action of combined antimicrobials.

The duration of antimicrobial activity observed also exceeds that reported by other pre-clinical studies using different technologies to prevent PSI. Such as Voos et al's (1999) tobramycin-impregnated polymethylmethacrylate pin sleeves which were evaluated using a goat model for 16 days, Greene et al's (2008) elution testing of chitosan coating containing gentamycin which demonstrated measurable releases for up to 96 hours and Qu et al's (2015) triclosan incorporation into sol-gel films deposited on percutaneous pins tested with elution testing for a period of 56 days.

Clindamycin and rifampicin were not detected in any samples following SPTT using HPLC analysis. As rifampicin content was substantially less than clindamycin and triclosan at the outset, increasing the concentration of rifampicin during the impregnation process may increase the rifampicin content in the collar, and thus increase the effect and duration of rifampicin activity. Further investigation is required on optimisation of drug content to establish the release rate of the combined antimicrobials over the duration of three months to ensure that the antimicrobial device is not reliant of triclosan monotherapy, and at subsequent risk of emerging bacterial resistance. The antimicrobial dosage used for the antimicrobial collars was an empirical decision based on the success of 0.2% (w/v) impregnation solution for combined clindamycin and rifampicin testing hydrocephalus shunts under flow conditions over 28 days (Bayston et al 1989). As the skin does not have clearance mechanisms that replicate flow

conditions it was anticipated that this dose would be effective in the antimicrobial collars.

Bacterial resistance was not observed with combined antimicrobial use in excess of three months, with the exception of corynebacteria, which were resistant to at least one of the antimicrobials, including triclosan. These findings concur with the dual drug principle (Zhao and Drlica 2001). Paradoxical resistance was observed at Day 56 for F1693 (*E coli*) with the combined antimicrobial collars, although not observed with single drug testing. As *E coli* is intrinsically resistant to rifampicin and clindamycin, the combined antimicrobial collar is reliant on triclosan alone, which predisposes it to resistance. The MIC of the resistant bacteria was not subsequently tested, though this would have indicated whether triclosan levels had become sub-inhibitory and resistant mutations developed.

SPTT is a useful test to determine the static diffusion of antimicrobials to create a ZoI against susceptible organisms (Bayston and Milner 1981; 1982) as well as determining the duration of activity due to the serial nature (Bayston et al 2009). However, SPTT does not reflect the clinical variances and conditions that may occur during an in-vivo trial. SPTT was tested only using a small sample of strains, although the antimicrobial effects of the collars would be expected to give similar results for other gram positive bacteria due to the broad spectrum of antimicrobial protection offered by the antimicrobial combination. Large ZoI suggest that the antimicrobial collars may prevent bacteria colonising the pin site, although it does not indicate protective activity in preventing bacterial attachment. The time taken for the antimicrobial agents to kill attached bacteria however was tested using tK100 (Bayston et al 2004).

TK100

Killing attached bacteria takes considerably longer than planktonic (Bayston et al 1997) especially as these often exhibit reduced antimicrobial susceptibility (Widmer et al 1991; Williams et al 1997). Results showed that antimicrobial discs eradicated between 92% and 100% of bacteria by 72 hours. The antimicrobial discs failed to kill F3592 (*S aureus*) by 72 hours, potentially due to the high clindamycin and rifampicin MICs for this strain. The collars did however maintain a ZoI with SPTT for over 90 days with F3592, indicating that the collars were able to inhibit bacterial growth, but were insufficient to kill attached bacteria. Any remaining bacteria are a potential infection risk, although patient factors also play an important protective role (Bayston 2009). The remaining six bacterial strains (F1693 *E coli*, F2903 *S aureus*, F2905 *Corynebacterium group G*, F3412 *Corynebacterium Jeikeium*, F3451 *S epidermidis* and F3501 *Corynebacterium macginleyi*) tested using tK100 methods were eradicated by 72 hours.

Similar impregnation technology has been successfully used with neurosurgical shunts impregnated with rifampicin and clindamycin to reduce clinical infection rates (Bayston et al 1989; Eymann et al 2008). However, tK100 is a static test with only one bacterial challenge. While it is unlikely that the pin site would be exposed to this level of bacterial contamination, further tests could include multiple challenges, or testing after SPTT to determine ability to kill bacteria after prolonged use. It is important to confirm eradication of attached bacteria, as failure would result in clinical failure and potentially delayed presentation of infection (Bayston et al 2004). Exudating pin sites may coat the surface of the collar and reduce the skin-collar contact and potentially reduce efficiency. Urinary conditioning films were studied as part of the PhD work conducted

by Fisher (2011), using similar antimicrobial technology. Fisher's work reported that the antimicrobial device was capable of killing bacteria in the presence of a urinary conditioning film.

Pin track model

The original model did not identify bacterial spread down the pin over a duration of three months when using the antimicrobial collar. The revised model however, demonstrated the ability of the collar to create a ZoI for F3592 (*S aureus*), and reduced bacterial tracking with F2903 (*S aureus*). This difference in results is likely to due to the increased sensitivity of the revised model and improved visibility of bacteria growth. While the bromoscesol model was able to detect bacterial growth in the control model using F2903, the subtle growth with the antimicrobial collar model may have been insufficient to visualise clearly or to cause colour change.

The control collar exacerbated bacterial tracking along the wire compared to the non-collar control. This may be due to the bacteria attaching to the collar and creating a source of growth, or potentially increasing the moisture collected under the collar expediting bacterial tracking along the wire. This reflects the findings by Clasper et al (2001b) which noted that fluid accumulation around the pin interface in an important factor in the spread of infection.

The ZoI achieved for F3592 is potentially due to bacteriostatic action rather than bactericidal due to higher bacterial MIC levels. The reduction in bacteria (F2903) tracking along the wire, when compared to the control, may allow patient factors to take an active role in eliminating the bacteria and further reduce the risk of infection and biofilm formation.

Again the pin track model represents static conditions and does not reflect clinical variations in which there may be repeated exposure to different organisms. It does however demonstrate that the collar is effective in reducing bacteria tracking along the pin/wire, and therefore is likely to reduce local colonisation and subsequent infection of the pins/wires. Further work should establish a quantitative measure for bacterial growth along the pin to allow for true comparison between products, or bacterial samples.

Scanning Electron Microscopy

As neither the researcher or SEM technician were blinded to the antimicrobial or control groups results are subject to detection and reporting bias. On examining the wires from the pin track model bacteria appeared to prefer the crevices of the stainless steel contour, though this may in part be due to bacteria being dislodged from external surfaces on removing the wire from the agar, thus affecting the number of bacteria visualised. Surface topography has been debated as a parameter which may influence microbial adhesion (El Abed et al 2012), potentially due to the increased surface area available for bacteria to attach. Bacterial attachment can also be affected by environmental elements and topography potentially may provide shelter from unfavourable environmental factors (Bohinc et al 2014). As this model was not designed to challenge bacterial growth, other than the presence of the antimicrobial collar, it is unlikely that this explains why bacteria are more apparent in fissures.

SEM is a useful technique to investigate surface structure and visualise bacteria and biofilm formation (El Abed et al 2012). Appearance of exopolysaccharide on F2903 control wires and both F3592 active and

control wires suggests biofilm formation and multiplication of bacteria. This concurs with pin track model findings that the antimicrobial collar did not prevent bacterial growth with F3592, although reduced the bacterial load in F2903. As SEM requires samples to be dehydrated, visualisation of exopolysaccharide layers can be affected due to their high water content. Techniques such as Environmental SEM permit examination of hydrated structures, and thus allows improved visualisation of exopolysaccharide structures, although bacteria may not be as clearly visualised due to the surrounding matrix. As objective measurement of biofilm structure or thickness was not required here further imaging was not undertaken, although it could be considered in future work.

Summary

The pre-clinical in-vitro tests have demonstrated the prolonged duration of the collar in maintaining a ZoI for sensitive isolates in excess of three months. The antimicrobial collar has also demonstrated that it can kill attached bacteria within 72 hours, and is expected to reduce the number of bacteria which may colonise the pin site or track down the pin to cause infection. This addressees the original study objectives which were to determine the effectiveness of antimicrobial collars against bacteria isolated from cases of PSI by means of in-vitro testing, while preventing bacterial resistance in the laboratory setting.

Impregnation process – reuse of solution

Production of multiple batches of antimicrobial collars using the same impregnation solution would have a significant impact on environmental costs of disposing of large quantities of solvents and antimicrobial waste products. There would also be added financial savings associated with the production costs of the collars, which would need to be considered as part of a detailed cost analysis.

The SPTT demonstrated that the combined antimicrobials gave a duration of activity which lasted for the 115 days tested. While there was a statistically significant difference in ZoI size between Batch 1 and Batch 5 collars, large zone sizes remained, suggesting that this may not be of clinical significance. Further tests should focus on the effectiveness of serial impregnations using different isolates and sensitivity profiles for SPTT and tK100 methods along with drug release studies.

4.5 Clinical testing

Patient and public involvement

PPI proved challenging due to a poor response from previous PPI volunteers and failure to attract new interest through NUH and CLARCH communications. Reasons cited for lack of response included perceived inability to contribute to due to the lack of knowledge and experience of external fixation. Initial communication and presentation styles may have influenced how the research was perceived by potential participants and affected the number of respondents, however as the invitation was sent via experienced PPI facilitators and communications teams, it is unlikely that this was a significant factor.

While large numbers of volunteers with personal knowledge and experience of external fixation devices were not anticipated, it was envisioned that respondents would offer general perspective which would have ensured research quality and relevance, and suitability of patient materials (INVOLVE 2012a). The small sampling frame generated through established routes was insufficient to create meaningful outcomes; therefore PPI results were generated from an opportunistic sample of service users, carers, members of staff and members of the public.

The patients and public involved with this consultation were those who were easiest to access and therefore not necessarily representative of the wider and more diverse population. The majority of participants involved with PPI activities reflected those groups who are more typically involved in public consultation activities: older, from white ethnic groups and from higher socio-economic backgrounds (INVOLVE 2012b, Pathways through participation 2009).

The results from the qualitative inquiry are not necessarily generalisable to other individuals, sites or health care settings outside of those studied (Cresswell 2009) or to wider populations (Parahoo 2006). The feedback presented however does portray a snap shot of the clinicians' and service users' thoughts regarding the antimicrobial collar. The value of this approach is the particularity not the generaliseability of findings (Green and Caracelli 1997) when exploring the perception, acceptability and usability of a novel antimicrobial device for PSI prevention.

Discussions surrounding the study, and use of an antimicrobial collar were favourable and generated interest and support at a local level. Discussions and testing of collar prototypes again were largely favourable, though highlighted some areas of concern, such as the fit and positioning of the

collars, and concerns regarding potential skin degradation and skin maceration underneath the collars. These concerns were noted and included as checks in the feasibility study. Following the short survey of patient and clinician preference concerning collar thickness, the 2mm thick collar was selected. Patient ability to apply, remove and care for the collars was monitored in the study to ensure that any difficulties were highlighted at an early stage

Qualitative research requires inductive data analysis to build from particulars to general themes making interpretations of the meaning of the data collected (Cresswell 2009). Limitations of the qualitative approach included potential bias from the researcher presenting the collars and recording the information from participants, as well as the small numbers of current service users interviewed. Strengths of this approach include the holistic approach to data collection and the ability of participants to form free ideas about the novel concept rather than have to choose from a predesigned response.

Feasibility study

Changes in local practice at the early stages of this project led to a reduction in the number of external fixator devices used during the study period. To ensure that maximum participants were identified, detailed information of the study was disseminated to the orthopaedic team and daily visits were made by the researcher to the orthopaedic trauma wards to facilitate discussion with members of the MDT and ward staff regarding the study. A major amendment to the study protocol was approved by the ethics committee on 23/9/13 to increase participant recruitment, although this was not sufficient to recruit the projected number of participants.

The objective of this study was to evaluate the safety and acceptability of the antimicrobial collar to participants. Participants and staff were receptive to the study, however issues concerning the antimicrobial collar affected participant compliance with the device. Based on poor adherence with the use of the antimicrobial collar during the feasibility study, progression to a full clinical trial is not currently recommended until further product development has occurred.

No safety concerns were identified during the feasibility study, however as only four participants continued to wear the collars for the duration of their treatment this would require further investigation after redesigning the collar. Following product development and further feasibility testing a multi-centred randomised control trial would be required in order to recruit sufficient participants for an adequately powered study.

From the samples obtained during the feasibility study, there was a statistically significant reduction in the number of bacteria identified at pin sites where the antimicrobial collar was present ($p<0.05$), particularly so for *S aureus*, CoNS and corynebacteria. This is an important observation, as these were the most commonly identified bacteria from the preceding bacterial evaluation, and the bacteria most commonly reported in the literature as causing infection (Antoci et al 2008, Marsh et al 1997, Jennison et al 2014, Rizvi et al 2011). As the aim of the antimicrobial collar is to prevent PSI, the reduction in bacteria isolated from insertion sites is of clinical importance. This would require further investigation following modification to the collar design to improve acceptability and compliance with use.

Lethaby et al (2013) have noted the insufficient evidence available to guide pin site care with studies reporting not statistically significant results (W-Dahl 2003, Egol et al 2006, Patterson 2005,) and utilising small sample sizes (Henry 1996, Camilo 2005, Cavusoglu 2009, Yuenyongviwat and Tangtrakulwanich 2011). Despite different aspects and combinations of pin site care PSI has not yet been reduced to 0% (Ktistakis et al 2015).

The antimicrobial collars where changed at three months to ensure continued antimicrobial delivery. In participants who complied with antimicrobial collar use only one participant was free from infection until frame removal (Day 182 - MS). For the remaining participants compliant with the antimicrobial collar the time till PSI varied from 21 days to 69 days. Future investigation of the antimicrobial collar should thus consider the time points at which infections occur (if any) in relation to the length of time the collar and external fixator have been in-situ.

It is possible that the current results are affected by the Hawthorne effect due to the research process (Torgerson and Torgerson 2008). This may have affected participant attitude to pin site care, subsequent infection rates, severity of infection or the general awareness of infection and speed in which infection was acted upon between hospital appointments. However, as the researcher spent similar time with each participant assessing pin sites and discussing recovery, similar Hawthorne effects will affect both groups (Torgeson and Torgeson 2008).

The potential for ascertainment bias also needs to be acknowledged in the study as blinding of the groups was not achievable due to the presence of the antimicrobial collar, and the principal investigator was responsible for randomisation, data collection and data analysis. The use of a suitable placebo (non-antimicrobial collar) would have overcome the suggestive

effect of the antimicrobial collar (Parahoo 2006) and reduced the risk of ascertainment bias, however due to the orange collar of the antimicrobial collars participants and clinicians could not have been adequately blinded to group allocation.

Open fractures are challenging injuries to manage and are noted to have significantly higher risk of infection and wound healing complications compared to closed injuries (Ryan and Pugliano 2013). Adequately powered studies would permit further analysis of patient groups and clear comparison between trauma and elective frame patients. With trauma patients particular areas of interest include open fracture injuries and the extent of nearby soft tissue injury in relation to PSI and bacteria identified. As prolonged use of percutaneous devices increases the risk of infection (Mason et al 2005, Hargreaves et al 2004) further work may consider swabbing pin sites at monthly intervals to determine how the bacterial load changes over time and how this correlates to infection rates and cross contamination of bacteria from other sites. This could also be linked to participant activities such as returning to work. Osteomyelitis managed with external fixation would also be an interesting group to include for further study to assess if they are at increased risk of PSI due to established infection.

The level of participant activity and rehabilitation would also have been a useful variable to consider in relation to infection, as Rogers et al (2007) suggested that increased activity and rehabilitation may lead to an increased risk of complications such as infection. Several of the participants returned to normal activities and routine as soon as possible. Three participants (OM, GB, SB) returned to employment activities with external fixator devices in-situ. Occupational activity varied from manual labour to office work. One participant (MC) redecorated several rooms

while in the external fixator device and one participant (MF) would walk or run several miles daily across local fields towards the end of the treatment period. Four of these participants (OM, GB, MC, MF) were randomised to the antimicrobial collar group, although were non-compliant with use. Of those who returned to normal daily activities only one participant (SB) did not experience signs of PSI, despite returning to manual labour and industrial manufacturing early on in the treatment period due to being self-employed.

Other areas for future study include the impact of infection on functional impairment and quality of life. Due to the longevity of treatment in some instances, it would be valuable to explore the impact of external fixation on mental health and self-care activities over the duration of treatment, and how these are affected by infection, or complications relating to overall external fixation management. Richards et al (2015) have reported paediatric participants developing depression and anxiety during limb reconstruction, although this has not yet been investigated in the same manner for the adult population. It would again be of interest to make these comparisons between trauma and elective frames.

Patient education regarding infection risk and potential consequences is an important issue that still needs addressing in clinical practice. Participants were reminded regularly by the researcher to clean pin sites using a clean-no-touch technique, but the majority of participants 'picked' crusts from around pin sites with unwashed hands, or 'squeezed' exudate from the pin sites, despite being strongly discouraged from touching insertion sites. Again this may have affected PSI and bacteria isolated due to repeated contamination of insertion sites and cross contamination from other pin sites, though this was equal for both study groups. Education was given throughout the treatment period to all participants, although in future, risk

of contamination may be more effectively reduced by covering insertion sites with sealed dressings to reduce temptation.

Future development of the antimicrobial collar should consider the use of the collar in combination with a sealed dressing to prevent the collar becoming displaced during daily activities, and prevent participant contamination of the pin sites. The use of a foam dressing such as Allevyn has the additional benefits of absorbing exudate and may be left in place for up to 7 days which is consistent with routine care advised by Timms et al (2011).

Participant evaluation of the collars

Overall the feedback from participants was positive and the majority of responses indicated that the collar was comfortable and did not cause irritation. Although all participants who completed the evaluation form considered the collar easy to apply the collar was noted to become displaced during normal activities. Further product development is required to minimise the likelihood of collars becoming unintentionally displaced. This may take the form of a more flexible silicone which would contour to the patient, or expanding the design of the collar to extend further up the pin for further security. Alternatively, an adhesive may be used to secure the edges of the collar, although this would make the collar harder to apply and remove, and constrain the functionality of being able to remove the collar and wash under the tap. The use of an additional clip to secure the collar in place may also reduce the likelihood of the collars being displaced.

Participant feedback also stated that the collars attracted dust and debris. While collars may be washed under the tap, it is preferable to prevent accumulation of debris. Strategies may include the use of an additional coating to reduce dust attachment, although this would need to be tested to ensure that the antimicrobial components can permeate the coating and remain effective. The use of an alternative material may also be an option, although this would require careful consideration and testing to determine if antimicrobials could be successfully impregnated, and delivered consistently over the required duration.

Of the study participants who completed the collar evaluation no-one disagreed with the statements that the collar was comfortable to use and did not cause irritation, although neutral scores were reported. Changing to an alternative or more pliable silicone may improve comfort, and should be considered as part of product development. No free text comments were given regarding comfort of the collar other than one participant describing the collar as being 'itchy' which would indicate local irritation caused by the collar.

Further product development should focus on retaining the collar in place, improving comfort and minimising the dust and debris that is attracted to the collar. No comments were made regarding the thickness of the collar and ease of application, although none of the participants independently managing pin sites were adversely affected by manual dexterity problems. Once the practical aspects of collar fitting and retention have been addressed the product can be more thoroughly evaluated in relation to the aesthetics, comfort and ease of use.

4.6 Patient evaluations

Patient experiences are an important factor of service evaluation and service improvement. Facilitating discussions concerning perceptions of health enables service users to express their thoughts and concerns. This not only improves communication between the patient and health care team, but offers a unique manner in which services can be evaluated.

Patient reported outcome measures

As patient requirements and expectations of health care interventions are often diverse it is important to understand patient concerns and priorities to ensure care is patient-centred (Rodrigues et al 2014). PROMs can provide a multidimensional aspect which takes into account the biopsychosocial aspects alongside work ability and quality of life (El Miedany 2014). These measures can be utilised to provide objectivity in subjective constructs (Haywood 2006). Traditional outcome measures developed by clinical experts may not reflect patient needs and opinions. Generic outcome tools may have low sensitivity and specificity which inhibits insight to patient expectations and consequently limits potential for service development (Rodrigues et al 2014). To ensure that PROMs have relevance to patients and are not biased by medical knowledge, outcome measures should be established though active discussion and patient participation.

The individualised approach to identifying PROMs for patients with external fixation allowed patients to identify unique combinations of outcomes. Due to the small number of patients in the sample, a limited number of responses were identified with a small spread of responses for each category, particularly for elective frames. It is evident that desired

outcome measures for many of the trauma patients were focused on physical recovery, with the main outcomes being return to normal activities (70%), and specifically the return to work for 45%. Interestingly, regaining the use of the affected limb was specified by only 30% as an outcome measure, but, this may have been an assumed outcome for those who specified outcomes of returning to normal activities. Although the number of elective frames were few, and the responses diverse, the main focus remained on pain and physical functioning. Unique outcomes were identified by those treated for infection or deformity and these therefore warrant further exploration.

Due to the varied circumstances in which external fixators are applied further work is required to establish separate outcomes for trauma and elective patients. This will facilitate greater understanding of the significance attached to each outcome measure. As the current review identified PROMs predominantly at the early stage of treatment it would also be of interest to follow patients through the continuum of care and identify how PROMs change through the course of treatment and assess at what point (if at all) outcomes are achieved. Likewise severity of injury, pathology or patient age and previous activity levels merit further exportation to determine if these correlate with given outcome measures.

As all patients received external fixation of the tibia, these findings are not generalisable to other external fixator devices such as halos. Two patients (both elective frames) had previous experience of external fixator devices. This may have altered expectation of treatment and outcomes, although responses given were comparable to other elective participants. Theming patient responses to condense categories may have been subject to researcher bias or the misinterpretation or overlooking of subtle differences in response, which were particular to each person's

expectation. The concept of measuring PROMs requires the application of scaling or graded responses. This aspect has not been considered at this stage in development.

Although standardized pre-determined questionnaires demonstrate reliability and consistency, they may omit issues which are important to patients, especially in specialised areas such as external fixation. The PROMs identified can be used to improve collaboration, communication and multidisciplinary working to enhance patient-centred care (Haywood 2006).

Patient Reported Experience Measures

PREMs provide insights into the interpersonal and technical quality of care (Haggerty 2010). The PREMs identified only relate to the hospital experience of patients with tibial frames and are therefore not representative of all patients with external fixator devices. Due to the time constraints of the study only patient experience of the hospital care was sought. It was not within the scope of the study to carry out a thematic review of patient experience living with a frame, though this would provide useful insight to patient experience.

The individualised approach to identifying experience measures allowed patients to identify unique measures by which they felt the service could be evaluated. PREMs provide a global view of service quality (Palmer and El Miedany 2014) and can be used to increase patient satisfaction (Otani et al 2005). From the small sample questioned, communication was considered to be a fundamental aspect of treatment, with the consultant being the key component to planning of care. Patients found that inconsistent and insufficient communication between the hospital (consultant) and community services made continuity of care difficult for community nurses and physiotherapists regarding what patients could do,

how much mobility/exercise was permitted, how to care for pin sites and what to do in the case of infection. Lack of contact details was also a key issue for several participants, who were unable to contact the hospital team for help and advice. In some instances patients needed to attend local hospitals for advice following falls or infection as they were unable to obtain advice from the treating centre.

Following identification of the lack of information available for patients, an information booklet was created which contained basic information about what to expect, and how to care for the frame, along with information of whom to contact (Appendix 14). This was formatted by the local Trust communications team and given to current service users for feedback on information and presentation. Feedback was positive with regard to clear information and presentation style and no further amendments were recommended.

The importance of peer support was highlighted by several participants. Despite improvements in trauma management, providing patient-centred care and psychosocial support still remains a challenge for trauma centres (Bradford et al 2011). The use of a peer support group may help improve self-management and timely access to information, however has not yet been set up at the host institution. Peer-support groups are available via social networking sites, although these lack the personal interaction which was viewed favourably.

It is important to recognise the individual within the health care system (Reay 2010) and their role in communicating the impact of disease and the effectiveness of healthcare (Palmer and El Miedany 2014). Current service assessment techniques commonly fail to include patient perspective and therefore inadequately inform clinical decision-making (Haywood 2006) and service development. Creating valid and reliable PREMs specific to department, disease or age will make patients central to quality improvements in care (Walker 2015).

Interventions aimed at reducing negative effects are more efficient for increasing patient satisfaction than those aimed at improving positive effects (Otani et al 2005). As patient satisfaction is influenced by varying standards, different expectations, the patients' disposition and previous experience (Haggerty 2010), it is important that traditional satisfaction measures are refined so that they can be combined with experience measures to benchmark care and service provision (Walker 2015).

Chapter 5 Summary

PSI is a common complication of external fixation which can cause osteomyelitis and delay fracture healing. PSI also incurs additional personal and financial losses for many individuals who are unable to return to normal activities as a result of additional treatment required. A reduction in PSI would therefore be of great benefit to the patient and reduce the complications and costs associated with infection.

To assess the potential market for a novel antimicrobial collar an electronic questionnaire was used to identify current clinical practices for pin site care. Responses highlighted diversity of practice across the UK despite the availability of current consensus guidelines. Pin site care was also varied internationally, which reflects the paucity of rigorous research in this field. Understanding the variation of bacteria present at pin sites is also an important step in developing a product to prevent PSI. Bacteria from clinically non-infected and clinically infected pins sites were isolated and tested for antimicrobial sensitivity. The largest group of PSI isolates belonged to the Staphylococcus genus, with *S aureus* being the most common species. The vast majority of isolates identified were sensitive to the antimicrobial combination of clindamycin, rifampicin and triclosan, and therefore the antimicrobial collar is expected to be effective in reducing PSI.

The in-vitro effectiveness of the antimicrobial collar was tested using a batch of test organisms identified from the PSI bacterial evaluation. Strains included *S aureus*, *S epidermidis* Corynebacteria and *E coli*. Serial Plate Transfer Testing demonstrated that antimicrobials were released for in excess of three months and able to produce a ZoI without signs of developing antimicrobial resistance. TK100 tests also demonstrated that

the impregnated silicone was able to eradicate attached bacteria within 72 hours and the pin track model confirmed the collars ability to reduce bacterial tracking below the surface and extending along the wire.

Although the feasibility study did not recruit the anticipated number of participants, it identified areas of product development to improve patient adherence and experience of using the collar. The limited data demonstrated that the antimicrobial collar significantly reduced the number of bacteria present at the pin site, in particular *S aureus*, CoNS and corynebacteria. Further research is required with an adequately powered trial to establish the clinical effectiveness of the antimicrobial collar in preventing PSI and the subsequent cost-benefit analysis, however acceptability of the device first needs to be improved before progression to clinical trial can be achieved.

To conclude, the current approach to managing pin sites has many deficiencies due to inconsistent practice and scanty rigorous research to determine best practice. Although large numbers of CoNS, *S aureus* and corynebacteria are found at non-clinically infected pin sites, the significant increase of *S aureus* identified in PSI suggests that this is a common causative organism. The in-vitro testing of the antimicrobial collar demonstrates its efficiency in maintaining a ZoI for over three months and ability to kill attached bacteria within 72 hours. Feasibility testing identified potential areas for product development to improve the collar, although preliminary results confirmed reduced bacterial numbers at pin sites where the collar remains in-situ. Redesign of the antimicrobial collar and further testing is recommended to determine the efficacy of the antimicrobial collar in preventing PSI.

References

Acar JF (2000) Antibiotic synergy and antagonism. *Medical Clinics of North America* 84(6), 1391-1406

Achermann Y, Goldstein EJ, Coenye T, Shirtliff ME (2014) Propionibacterium acnes: from commensal to opportunistic biofilm associated implant infection. *Clinical Microbiology Reviews* 27(3), 419-440

Ahlborg HG and Josefsson PO (1999) Pin-tract complications in external fixation of fractures of the distal radius. *Acta Orthopaedica* 70(2), 116-118

Akobeng, AK (2005) Understanding randomised controlled trials. *Archives of Disease in Childhood* 90(8), 840-844

Antoci V, Ono CM, Antoci Jr V and Raney EM (2008) Pin-tract infection during limb lengthening using external fixation. American Journal of Orthopedics 37(9), E150-E154

Arvaniti K, Lathyris D, Clouva-Molyvdas P, Haidich, AB, Mouloudi E, Synnefaki E, Koulourida V, Georgopoulos D, Gerogianni N, Nakos G. Matamis D (2012) Comparison of Oligon catheters and chlorhexidine-impregnated sponges with standard multilumen central venous catheters for prevention of associated colonization and infections in intensive care unit patients: A multicenter, randomized controlled study. *Critical Care Medicine* 40(2), 420-429

Barriere SL (2006) Protein synthesis, inhibitors, fluoroquinolones, and rifampin for biofilm infections in *Biofilms, infection and antimicrobial therapy* by Pace, JL, Rupp ME, Finch RG. (Editors) Taylor and Francis, Boca Raton p352-362

Bartlett JG, Sutter VL and Finegold SM (1972) Treatment of anaerobic infections with lincomycin and clindamycin. *New England Journal of Medicine* 287(20), 1006-1010

Basak P, Adhikari B, Banerjee I & Maiti, TK (2009) Sustained release of antibiotic from polyurethane coated implant materials. *Journal of Materials Science: Materials in Medicine* 20(1), 213-221

Basbozkurt M, Yildiz C, Komurcu M, Demiralp B, Kurklu M and Atesalp AS. (2005) Management of fibula hemimelia with Ilizarov circular external fixator. *Acta Orthopaedica et Traumatologica Turcica* 39(1), 46-53

Battle J and Carmichael KD (2007) Incidence of pin track infections in children's fractures treated with Kirschner wire fixation. Journal of Paediatric Orthopaedics 27(2), 154-157

Bayston, R (1978) Use of polyvinylpyrrolidone in testing of staphylococci for sensitivity to methicillin and cephradine. *Journal of Clinical Pathology* 31(5), 434-436

Bayston R and Milner RDG (1981) Antimicrobial activity of silicone rubber used in hydrocephalus shunts, after impregnation with antimicrobial substances. *Journal of Clinical Pathology* 134(9), 1057-1062

Bayston R and Milner RD (1982) The sustained release of antimicrobial drugs from bone cement. *The Journal of Bone and Joint Surgery* 64B(4), 460-464

Bayston R, Grove N, Siegel J, Lawellin D and Barsham S (1989) Prevention of hydrocephalus shunt catheter colonisation in vitro by impregnation with antimicrobials. *Journal of Neurology, Neurosurgery & Psychiatry* 52(5), 605-609

Bayston R and Lambert E (1997) Duration of protective activity of cerebrospinal fluid shunt catheters impregnated with antimicrobial agents to prevent bacterial catheter-related infection. *Journal of Neurosurgery* 87(2), 247-251

Bayston R, Ashraf W, and Bhundia C (2004) Mode of action of an antimicrobial biomaterial for use in hydrocephalus shunts. *Journal of Antimicrobial Chemotherapy* 53(5), 778-782

Bayston R (2007a) Bactiseal: A system to prevent catheter infections in shunts and external ventricular drains. *British Journal of Neuroscience Nursing* 3(11), 526-531

Bayston R, Ashraf W, Smith T (2007b) Triclosan resistance in methicillin-resistant Staphylococcus aureus expressed as small colony variants: a novel mode of evasion of susceptibility to antiseptics. *Journal of Antimicrobial Chemotherapy* 59(5), 848–853

Bayston R, Fisher LE, Weber K (2009) An antimicrobial modified silicone peritoneal catheter with activity against both Gram positive and Gram negative bacteria. *Biomaterials* 30(18), 3167-3173

Bayston R, Vera L, Mills A, Ashraf W, Stevenson O, Howdle SM (2010) In vitro antimicrobial activity of silver-processed catheters for neurosurgery. *Journal of Antimicrobial Chemotherapy* 65; 258-265

Bernard K (2012) The genus Corynebacterium and other medically-relevant, coryneform like bacteria. *Journal of Clinical Microbiology*, JCM-00796.

Bhargava HN and Leonard PA (1996) Triclosan: Applications and safety. *American Journal of Infection Control* 24(3), 209–218

Blum AL, Bongiovanni JC, Morgan SJ, Flierl MA and dos Reis FB (2010) Complications associated with distraction osteogenesis for infected nonunion of the femoral shaft in the presence of a bone defect: A retrospective series. *Journal of Bone Joint Surgery* 92B(4), 565-570

Bobulsky GS, Al-Nassir WN, Riggs MM, Sethi AK and Donskey CJ (2008) Clostridium difficile skin contamination in patients with C. difficile–associated disease. *Clinical Infectious Diseases* 46(3), 447-450

Bohinc K, Dražić G, Oder M, Jevšnik M, Nipič D, Godič-Torkar,K, & Raspor P (2014) Available surface dictates microbial adhesion capacity. *International Journal of Adhesion and Adhesives* 50, 265-272

Boersma RS, Jie KS, Verbon A, Van Pampus EC and Schouten HC (2008) Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies. Annals of Oncology 19(3), 433-442

Bossetti M, Massè A, Tobin E and Cannas M (2002) Silver coated materials for external fixation devices: in vitro biocompatibility and genotoxicity. *Biomaterials* 23(3), 887-892.

Bradford AN, Castillo RC, Carlini AR, Wegener ST, Teter Jr H and Mackenzie EJ (2011) The trauma survivors network: Survive. Connect. Rebuild. *Journal of Trauma and Acute Care Surgery* 70(6), 1557-1560

British Society for antimicrobial chemotherapy (2014) BSAC methods for antimicrobial testing. Version 13 June 2014.

Britten S, Ghoz A and Duffield B, Giannoudis P (2013) Ilizarov fixator pin site care: The role of crusts in the prevention of infection. *Injury* 44(10), 1275-1278.

Calfee RP and Adams AA (2013) Clinical research and patient-rated outcome measures in hand surgery. *The Journal of Hand Surgery* (4); 851-855

Camathias C, Valderrabano V and Oberli H (2012) Routine pin tract care in external fixation is unnecessary: A randomised prospective, blinded controlled study. *Injury* 43(11), 1969-1973.

Camilo AM, and Bongiovanni JC (2005) Evaluation of effectiveness of 10% polyvinylpyrrolidone-iodine solution against infections in wire and pin holes for Ilizarov external fixators. *Sao Paulo Medical Journal* 123(2), 58-61

Campbell AA, Song L, Li, XS, Nelson BJ, Bottoni C, Brooks DE, and DeJong ES (2000) Development, characterization, and anti-microbial efficacy of hydroxyapatite-chlorhexidine coatings produced by surface-induced mineralization. *Journal of Biomedical Materials Research* 53(4), 400-407

Campoccia D, Montanaro L and Arciola CR (2006) The significance of infection related to orthopaedic devices and issues of antibiotic resistance. *Biomaterials* 27(11), 2331-2399

Capper M, Soutis C and Oni OO (1994) Comparison of the stresses generated at The pin-bone interface by standard and conical fixator pins. *Biomaterials* 15(16,; 471-473

Catagni MA, Ottaviani G, Combi A and Elhence A (2006) External circular fixation: A comparison of infection rates between wires and conical half-pins with threads outside or inside the skin. *Journal of Trauma and Acute Care* 61(5), 1186-1191

Cavusoglu AT, Er MS, Inal S, Ozsoy MH, Dincel VE, Sakaogullari A (2009) Pin site care during external fixation using two different protocols. *Journal of Orthopaedic Trauma* 23(10), 724-730

Chan CK, Saw A, Kwan MK, Karina R (2009) Diluted povidone-iodine versus saline for dressing metal-skin interfaces in external fixation. *Journal of Orthopaedic Surgery* 17(1), 19-22

Charnley J (1951) Compression arthrodesis of the ankle and shoulder. *Journal of Bone & Joint Surgery* 33B(2), 180-191

Charnley J and Low HG (1958) A study of the end results of compression arthrodesis. *Journal of Bone Joint Surgery* 40B(4), 633-635

Checketts RG and Otterburn M (1992) Pin tract infection: Definition, prevention, incidence. Abstracts of the 2nd Riva Congress, University of Verona and University of Montpellier, Riva di Garda, Italy 98–99

Checketts RG, Otterburn M, and MacEachern G (1993) Pin track infection: definition, incidence and prevention. *International Journal of Orthopaedic Trauma* 3(Suppl 3), 16-18

Chen W, Oh S, Ong AP, Oh N, Liu Y, Courtney HS, Appleford M and Ong JL (2007) Antibacterial and osteogenic properties of silver-containing hydroxyapatite coatings produced using a sol gel process. *Journal of Biomedical Materials Research Part A* 82(4), 899-906.

Chou TG, Petti CA, Szakacs J and Bloebaum RD (2010) Evaluating antimicrobials and implant materials for infection prevention around transcutaneous osseointegrated implants in a rabbit model. *Journal of Biomedical Materials Research Part A* 92(3), 942-952

Chuanchuen R, Karkhoff-Schweizer RR, and Schweizer HP (2003) High-level triclosan resistance in pseudomonas aeruginosa is solely a result of efflux. *American Journal of Infection Control* 31(2), 124-127

Ciusa ML, Furi L, Knight D, Decorosi F, Fondi M, Raggi C, Coelho JR, Aragones L, Moce L, Visa P, Freitas AT, Baldassarri L, Fani R, Viti C, Orefici G, Martinez JL, Morrissey I, Oggioni M (2012) A novel resistance mechanism to triclosan that suggests horizontal gene transfer and demonstrates a potential selective pressure for reduced biocide susceptibility in clinical strains of Staphylococcus aureus. *International Journal of Antimicrobial Agents* 40(3), 210-220

Clasper JC, Parker SJ, Simpson AH and Watkins PE (1999) Contamination of the medullary canal following pin-tract infection. *Journal of Orthopaedic Research* 17(6), 947-952

Clasper JC, Cannon LB, Stapley SA, Taylor VM and Watkins PE (2001b) Fluid accumulation and the rapid spread of bacteria in the pathogenesis of external fixator pin track infection. *Injury* 32(5), 377-381

Clint SA, Eastwood DM, Chasseaud M, Calder PR and Marsh DR (2010) The "Good, Bad and Ugly" pin site grading system: A reliable and memorable method for documenting and monitoring ring fixator pin sites. *Injury* 41(2), 147-150

Coester LM, Nepola JV, Allen J and Marsh L (2006) The effects of silver coated external fixation pins. *Iowa Orthopaedic Journal* 26, 48-53

Creswell JW (2009) *Research design: Qualitative, quantitative and mixed methods approaches.* Third edition. Sage, Los Angeles

Cutting K and Harding K (1994) Criteria for identifying wound infection. *Journal of Wound Care* 3, 198-201

Dahl MT, Guli B and Berg T (1994) Complications of limb lengthening – A learning curve. *Clinical Orthopaedics Related Research* 301,10-18

Davis R, Holt N and Nayagam S (2005) The care of pin sites with external fixation. *Journal of Bone and Joint Surgery* 87B(5), 716-719

Dayton P, Prins DB, Hensley N, Wienke J (2011) A user friendly method of pin site management for external fixators. *Foot & Ankle Specialist* 4, 370-372

De Bastiani G, Aldegheri R and Brivio LR (1984) The treatment of fractures with a dynamic axial fixator. *Journal of Bone & Joint Surgery* 66B(4), 538-45

De Silva D (2013) *Evidence scan: Measuring patient experience.* The Health Foundation http://www.health.org.uk/public/cms/75/76/313/4300/Measuring%20patient%20experience.pdf?realName=7qM8Wm.pdf

Department of Health (2005) *Research Governance Framework,* 2nd Edition. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

Department of Health (2010) *Equity and excellence: Liberating the NHS.* London, The Stationery Office. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/228836/7432.pdf

Dhanalakshmi TA, Umapathy BL, and Mohan DR (2012) Prevalence of inducible clindamycin resistance in Staphylococcus aureus. *Journal of Academy of Medical Sciences* 2(2), 73

Donlan RM (2009) Preventing biofilms of clinically relevant organisms using bacteriophage. *Trends in Microbiology* 17(2), 66-72

Donlan RM and Costerton JW (2002) Biofilms: Survival mechanisms of clinically relevant microorganisms. *Clinical Microbiology Reviews* 15(2), 167-193

Donlan RM (2001) Biofilms and device-associated infections. *Emerging Infectious Diseases* 7(2), 277

Donskey CJ (2010) Preventing transmission of Clostridium difficile: is the answer blowing in the wind? *Clinical Infectious Diseases* 50(11), 1458-1461

Drlica K (2003) The mutant selection window and antimicrobial resistance. *Journal of Antimicrobial Chemotherapy* 52(1), 11-17

Edwards A, Ramaswamy R and Bradish C (2002) Notes on the practicalities of circular frame treatment for limb lengthening and deformity correction in children. Journal of Orthopaedic Nursing 6(4), 198-203

Edwards NC, Engelhart L, Casamento EM, and McGirt MJ (2015). Cost-consequence analysis of antibiotic-impregnated shunts and external ventricular drains in hydrocephalus. *Journal of Neurosurgery* 122(1), 139-147

Egol KA, Paksima N, Puopolo S, Klugman J, Hiebert R and Koval KJ (2006) Treatment of external fixation pins about the wrist: A prospective, randomized trial. *Journal of Bone Joint Surgery* 88A(2), 349-354

El Abed S, Hamadi, F, Latrache, H and Ibnsouda SK (2012) Scanning electron microscopy (SEM) and environmental SEM: suitable tools for study of adhesion stage and biofilm formation. *INTECH* Open Access Publisher

Elek SD, & Conen PE (1957) The virulence of Staphylococcus pyogenes for man. A study of the problems of wound infection. *British Journal of Experimental Pathology* 38(6), 573

El Miedany Y (2014) Adopting patient-centered care in standard practice: PROMs moving toward disease-specific era. *Clinical and Experimental Rheumatology* 32(5), S40-S46

El-Mowafi H (2004) Assessment of percutaneous V osteotomy of the calcaneous with Ilizarov application for correction of complex foot deformities. *Acta Orthopaedical Belgica* 70(6), 586-590

European Medicines Agency (2001) *Choice of Control Group in Clinical trials*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf

Eymann R, Chehab S, Strowitzki M, Steudel WI and Kiefer M (2008) Clinical and economic consequences of antibiotic impregnated cerebrospinal fluid shunt catheters. *Journal of Neurosurgery Pediatrics* 1, 444-450

FDA (2008) Vancomycin solubility study. Food and Drug www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082291.pdf

Fiebelkorn KR, Crawford SA, McElmeel ML, Jorgenson JH (2003) Practical disk diffusion method for detection of inducible clindamycin resistance in staphylococcus aureus and coagulase-negative staphylococci. *Journal of Clinical Microbiology* 41(10), 4740-4744

Fisher LE, Hook AL, Ashraf W, Yousef A, Barrett DA, Scurr DJ, Chen X, Smith EF, Fay M, Parmenter CD, Parkinson R, Bayston (2015) Biomaterial modification of urinary catheters with antimicrobials to give long-term broad spectrum antibiofilm activity. *Journal of Controlled Release* 202; 57-64

Fisher L (2011) *Development and evaluation of an antimicrobial urinary catheter.* Thesis. University of Nottingham.

Forrest GN and Tamura K (2010) Rifampin combination therapy for nonmycobacterial infection. *Clinical Microbiology Reviews* 23(1), 14-34

Forster H, Marotta JS, Heseltine K, Milner R and Jani S (2004) Bacterial activity of antimicrobial coated polyurethane sleeves for external fixator pins. *Journal of Orthopaedic Research* 22(3), 671-677

Fragomen AT and Rozbruch SR (2007) The mechanics of external fixation. *HSS Journal* 3(1), 13-29

Ganser A, Thompson R, Tami I, Neuhoff D, Steiner A and Ito K (2007) An in vivo experimental comparison of stainless steel and titanium schanz screw for external fixation. *European Journal of Trauma and Emergency Surgery* 33(1), 59-68

Gardner SE, Frantz RA, Doebbeling BN (2001) The validity of the clinical signs and symptoms used to identify localized chronic would infection. *Wound Repair and Regeneration* 9(3), 178-186

Glen L, Ismail N, Ashraf W, Scammell B and Bayston R (2012) Localisation and identification of bacteria in the skin of patients undergoing primary knee and hip replacement surgery after surgical skin preparation. *Journal of Bone & Joint Surgery* 94B(S), 160

Gohel K, Jojera A, Soni S, Gang S, Sabnis R, and Desai M (2014) Bacteriological profile and drug resistance patterns of blood culture isolates in a tertiary care nephrourology teaching institute. *BioMed Research International*, http://www.hindawi.com/journals/bmri/2014/153747/cta/

Goldstein BP (2014) Resistance to rifampicin: A review. *The Journal of Antibiotics* 67(9), 625-630

Gordon JE, Kelly-Hahn J, Carpenter CJ and Schoenecker PL (2000) Pin site care during external fixation in children: Results of a nihilistic approach. *Journal of Paediatric Orthopaedics* 20(2), 163-165

Grant S, Kerr D, Wallis M and Pitchford D (2005) Comparison of povidone-iodine solution and soft white paraffin ointment in the management of skeletal pin-sites: A pilot study. *Journal of Orthopaedic Nursing* 9(4), 218-225

Greene JC. And Caracelli VJ. (Editors) (1997) *Advances in mixed-method evaluation: The challenges and benefits of integrating diverse paradigms.* San Francisco. Jossey-Bass

Greene AH, Bumgardner JD, Yang Y, Moseley J, and Haggard WO (2008) Chitosan-coated stainless steel screws for fixation in contaminated fractures. *Clinical Orthopaedics and Related Research* 466(7), 1699-1704

Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, Bouffard GG, Blakesley RW, Murray PR, Green ED, Turner ML, Segre JA (2009) Topographical and temporal diversity of the human skin microbiome. *Science* 324(5931), 1190–1192

Guzel A, Ozekinci T, Ozkan U, Celik Y, Ceviz A and Belen D (2009) Evaluation of the skin flora after chlorhexidine and povidone-iodine preparation in neurosurgical practice. *Surgical Neurology* 71(2), 207-210

Gwent KL (2014) *Handbook of Inter-rater reliability*. Fourth Edition. Advanced Analytics, Gaithersburg.

Haggerty JL (2010) Are measures of patient satisfaction hopelessly flawed? *British Medical Journal* 341(4783), 790

Hargreaves DG, Drew SJ and Eckersley R (2004) Kirchner wire pin tract infection rates: A randomised controlled trial between percutaneous and buried wires. *Journal of Hand Surgery* 29B(4), 374-376

Harrington AT, Mizuki S, Bui U and Clarridge JE (2014) Hardware infection with Corynebacterium spp: A case report and review of the literature. *Clinical Microbiology Newsletter* 36(2), 9-13

Haywood KL (2006) Patient-reported outcome I: Measuring what matters in musculoskeletal care. *Musculoskeletal Care* 4(4), 187-203

Health and Social Care Information Centre (2014) *Provisional monthly patient reported outcome measures (PROMs) in England: A guide to PROMs methodology*. HSCIC www.hscic.gov.uk/media/1537/A-Guide-to-PROMs-Methodology/pdf/PROMs_Guide_V8.pdf

Health Research Authority (2009) Defining research. Health Research Authority, London www.hra.nhs.uk/documents/2013/09/defining-research.pdf

Hedin H and Larsson S (2004) Technique and considerations when using external fixation as a standard treatment of femoral fractures in children. *Injury* 35(12), 1255-1263

Henry C (1996) Pinsites: Do we need to clean them? *Practice Nursing* 7(4), 12–7

Hetrick EM and Schoenfisch MH (2006) Reducing implant-related infection: Active release strategies. *Chemical Society Reviews* 35(9), 780-789

Hoffman K, Cole E, Playford ED, Grill E, Soberg HL and Brohi K (2014) Health outcome after major trauma: What are we measuring? *PLoS ONE* 9(7) www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0103082&representation=PDF

Hoonakker P and Carayon P (2009) Questionnaire survey nonresponse: A comparison of postal and internet surveys. *International Journal of Human-Computer Interaction* 25(3), 348-373

Hosny GA (2005) Unilateral humeral lengthening in children and adolescents. *Journal of Paediatric Orthopaedics* 14B(6), 439-443

Human Microbiome Project Consortium (2012) Structure, Function and diversity of the healthy human microbiome. *Nature* 486(7402), 207-214

Hutchinson DT, Bachus KN and Higgenbotham T (2000) External fixation of the distal radius: To predrill or not to predrill. *The Journal of Hand Surgery* 25A(6), 1064-1068

Ibnoulkhatib A, Lacroix J, Moine A, Archambaud M, Bonnet E. and Laffosse JM (2012) Post-traumatic bone and/or joint limb infections due to Clostridium spp. *Orthopaedics & Traumatology: Surgery & Research* 98(6), 696-705

Inan M, Bomae JD, Kucukkaya M and Harma A (2004) A comparison between the use of a monolateral external fixator and the Ilizarov technique for pelvic support osteotomies. *Acta Orthopaedica Traumatologica Turcica* 38(4), 252-260

International Labour Organisation (2007) *International Standard Classification of Occupants ISCO-08.* http://www.ilo.org/public/english/bureau/stat/isco/docs/resol08.pdf

INVOLVE (2012a) *Briefing notes for researchers: public involvement in NHS, public health and social care network*. INVOLVE, NIHR, Hampshire

INVOLVE (2012b) *Diversity and inclusion: What's it all about and why is it important for public involvement in research?* INVOLVE, NIHR, Hampshire.

James G, Hartley JC, Morgan RD, and Ternier J (2014) Effect of introduction of antibiotic-impregnated shunt catheters on cerebrospinal fluid shunt infection in children: a large single-center retrospective study: Clinical article. *Journal of Neurosurgery: Pediatrics* 13(1), 101-106.

Jennison T, McNally M and Pandit H (2014) Prevention of infection in external fixator pin sites. *Acta Biomaterialia* 10(2), 595-603

Kao HK, Chen MC, Lee WC, Yang WE, and Chang CH (2014) A prospective comparative study of pin site infection in pediatric supracondylar humeral fractures: daily pin care vs. no pin care. *Archives of Orthopaedic and Trauma Surgery* 134(7), 919-923

Karnezis I, Miles A, Cunningham J and Learmonth, I (1999) Axial preload in external fixator half-pins: A preliminary mechanical study of an experimental bone anchorage system. *Clinical Biomechanics* 14(1), 69-73

Katsenis D, Bhave A, Paley D and Herzenberg JE (2005) Treatment of malunion and nonunion at the site of an ankle fusion with the Ilizarov apparatus. *Journal of Bone and Joint Surgery* 87A(2), 302-309

Key J (1932) Positive pressure in arthrodesis for tuberculosis of the knee joint, South Med Journal 25; 909-915 cited in Salem KH, Keppler P, Kinzl L and Schmelz A. (2006) Hybrid external fixation for arthrodesis in knee sepsis. *Clinical Orthopaedics and Related Research* 451, 113-120

Klimo Jr,P, Thompson CJ, Baird LC, and Flannery AM (2014) Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 7: Antibiotic-impregnated shunt systems versus conventional shunts in children: a systematic review and meta-analysis. *Journal of Neurosurgery: Pediatrics* 14(Suppl 1), 53-59

Kim J, Pitts B, Stewart PS, Camper A and Yoon J (2008) Comparison of the antimicrobial effects of chlorine, silver ions and tobramycin on biofilm. *Antimicrobial Agents and Chemotherapy* 52(4), 1446-1453

Kleiner E, Monk AB, Archer GL, and Forbes BA (2010) Clinical significance of Staphylococcus lugdunensis isolated from routine cultures. *Clinical Infectious Diseases* 51(7), 801-803

Kluytmans J, Van Belkum A, and Verbrugh H (1997) Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks. *Clinical Microbiology Reviews* 10(3), 505-520

Kocaoğlu M, Eralp L and Tomak Y (2001) Treatment of humeral shaft non-unions by the Ilizarov method. *International Orthopaedics* 25(6), 396-400

Krishna BV and Gibb AP (2010) Use of octenidine dihydrochloride in meticillin-resistant Staphylococcus aureus decolonisation regimens: A literature review. *Journal of Hospital Infection* 74(3), 199-203

Ktistakis I, Guerado E, and Giannoudis PV (2015) Pin-site care: Can we reduce the incidence of infections? *Injury* 46, S35-S39

Latimer J, Forbes S and McBain AJ (2012) Attenuated virulence and biofilm formation in staphylococcus aureus following sublethal exposure to triclodan. *Antimicrobial Agents and Chemotherapy* 56(6), 3092-3100

Lee P, Li PC, Liu CH and Hsieh CL (2011) Test-retest reliability of two attention tests in schizophrenia. *Archives of Clinical Neuropsychology* 26, 405-411

Lee CK, Chua YP, Saw A (2012) Antimicrobial gauze as a dressing reduces pin site infection. *Clinical Orthopaedics and Related Research* 470(2), 610–15.

Lee-Smith J, Santy J, Davis P, Jester R and Kneale J (2001) Pin site management – towards a consensus: Part 1. *Journal of Orthopaedic Nursing* 5(1), 37-42

Lerner A, Chezar A, Haddad M, Kaufman H, Rozen H and Stein H (2005) Complications encountered while using thin-wire-hybrid-external fixation modular frames for fracture fixation: A retrospective clinical analysis and possible support for "Damage control orthopaedic surgery". *Injury* 36(5), 590-598

Lethaby A, Temple J and Santy J (2013) *Pin site care for preventing infections associated with external bone fixators and pins*, Cochrane Database of Systematic Reviews, Issue 12, Oxford: John Wiley and Sons

Levy CW, Roujeinikova A, Sedelnikova S, Baker PJ, Stuitje AR, Slabas AR, Rice DW, and Rafferty JB (1999) Molecular basis of triclosan activity. *Nature* 398(6726), 383-384

Lewis JS, & Jorgensen JH (2005) Inducible clindamycin resistance in staphylococci: should clinicians and microbiologists be concerned? *Clinical Infectious Diseases* 40(2), 280-285

Li H, Ogle H, Jiang B, Hagar M and Li B (2010) Cefazolin embedded biodegradable polypeptide nanofilms promising for infection prevention: A preliminary study on cell responses. *Journal of Orthopaedic Research* 28(8), 992-999

Limb M (2003) Psychological issues relating to external fixation of fractures. *Nursing Times* 99(44), 28

Limb M (2004) An evaluation survey of self concept issues in adult client undergoing limb reconstruction procedures. *Journal of Orthopaedic Nursing* 8(1), 34-40

Liu SJ, Wen-Neng Ueng S, Lin SS, and Chan EC (2002) In vivo release of vancomycin from biodegradable beads. *Journal of Biomedical Materials Research* 63(6), 807-813

Lory S (2014) The family Staphyloccaceae in *The Prokaryotes*, Springer, Bermin Heidelberg pp363-366

Medicines and Healthcare Research Agency (MHRA) (2012) *Drug safety update. Chlorhexidine: reminder of potential for hypersensitivity* http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON140701

Medicines and Healthcare Research Agency (MHRA) (2012b) *Medical Device Alert Ref MDA/2012/075* http://www.mhra.gov.uk/home/groups/dts-bs/documents/medicaldevicealert/con197920.pdf

McMurry LM, Oethinger M, and Levy SB (1998) Triclosan targets lipid synthesis. *Nature* 394(6693), 531-532

Marangoz S, Feldman DS, Sala DA, Hyman JE and Vitale MG (2008) Femoral deformity correction in children and young adults using Taylor spatial frame. *Clinical Orthopaedic Related Research* 466(12), 3018-3024

Marsh D, Shah S, Elliott J, Kurdy N (1997) The Ilizarov method in non-union, malunion and infection of fractures. *Journal if Bone & Joint Surgery* 79B(2); 273-279

Mason WTM, Khan SN, James CL, Chesser TJS and Ward AJ (2005) Complications of temporary and definitive external fixation of pelvic ring fractures. *Injury* 36(5);599-604

Merck Manual: Professional edition (2014) *Clindamycin* http://www.merckmanuals.com/professional/lexicomp/clindamycin.html

Montanaro L, Campoccia D and Arciola C (2007) Advancements in molecular epidemiology of implant infections and future perspectives. *Biomaterials* 28(34), 5155-5168

Moriarty TF, Schlegel U, Perren S and Richards RG (2010) Infection in fracture fixation: Can we influence infection rates through implant design? Journal of Materials Science: *Materials in Medicine* 21(3), 1031-1035

Moroni A, Aspenberg P, Toksvig-Larsen S, Falzaranno G and Giannini S (1998) Enhanced fixation with hydroxyapatite coated pins. *Clinical Orthopaedics and Related Research* 346, 171-177

Moroni A, Heikkila J, Magyar G and Toksvig-Larsen S (2001) Fixation strength and pin tract infection of hydroxyapatite-coated tapered pins. *Clinical Orthopaedic Related Research* 388, 209-217

Moroni A, Faldini C, Pegreffi F and Giannini S (2002a) Fixation strength of tapered versus bicylindrical hydroxyapatite-coated external fixation pins: An animal study. *Journal of Biomedical Materials Research* 63(1), 61-64

Moroni A, Vabbibi F, Mosca M and Gianmmini S (2002b) Techniques to avoid pin loosening and infection in external fixation. *Journal of Orthopaedic Trauma* 16(3), 189-195

Morris AB, Brown RB, and Sands M (1993) Use of rifampin in nonstaphylococcal, nonmycobacterial disease. *Antimicrobial Agents and Chemotherapy,* 37(1), 1-7

Mullen PM (1999) Public involvement in health care priority setting: An overview of methods for eliciting values. *Health Expectations* 2(4), 222-234

Munckhof W, Sleinschmidt S and Turnidge J (2004) Resistance development in community-acquired strains of methicillin-resistant Staphylococcus aureus: an in vitro study. *International Journal of Antimicrobial Agents*. 24(6), 605-608

Nakase T, Kitano M, Kawai H, Ueda T, Higuchi C, Hamada M and Yoshikawa H (2009) Distraction osteogenesis for correction of three-dimensional deformities with shortening of lower limbs by Taylor Spatial Frame. *Archives of Orthopaedic Trauma Surgery* 129(9), 1197-1201

Narayan B and Marsh DR (2003) The Ilizarov method in the treatment of fresh fractures. Curr Orthop 17;447-457

Norrish A, Lewis C and Harrison W (2007) Pin-track infection in HIV-positive and HIV-negative patient with open fractures treated by external fixation: A Prospective, blinded, case-controlled study. *Journal of Bone and Joint Surgery* 89B(6), 790-793

Nulty DD (2008) The adequacy of response rates to online and paper surveys: What can be done? *Assessment and evaluation in Higher Education* 33(3), 301-314

Ogbemudia AO, Bafor A, Ogbemudia EJ, and Edomwonyi E (2015) Efficacy of 1% silver sulphadiazine dressings in preventing infection of external fixation pin-tracks: a randomized study. *Strategies in Trauma and Limb Reconstruction* (10)2, 1-5

Oh J, Freeman AF, Park M, Sokolic R, Candotti F, Holland SM, and Kong HH (2013) The altered landscape of the human skin microbiome in patients with primary immunodeficiencies. *Genome Research* 23(12), 2103-2114

Oliver SR, Rees RW, Clarke-Jones L, Milne R, Oakley AR, Litt D, Gabbay J, Stein K, Buchanan P and Gyte G (2008) A multidimensional conceptual framework for analysing public involvement in health services research. *Health Expectations* 11(1), 72-84

Otani K, Kurz RS, Harris LE, Byrne FD, and Otani K (2005) Managing primary care using patient satisfaction measures/practitioner application. *Journal of Healthcare Management* 50(5), 311-325

Oudiz RJ, Widlitz A, Beckmann XJ, Camanga D, Alfie J, Brundage BH, and Barst RJ (2004) Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. *CHEST Journal* 126(1), 90-94

Paley D and Jackson RW (1985) Surgical scrub sponges as part of the traction apparatus: An alternative to pin site care to reduce pin track infection, *Injury* 16 (9), 605-606

Palmer D and El Miedany YE (2014) PREMs in inflammatory arthritis: from guidelines to standard practice" *British Journal of Nursing* 23(18), 982-985

Papagelopoulos P, Sapkas G, Kateros K, Papadakis S, Vlamis J and Falagas M (2001) Halo pin intracranial penetration and epidural abscess in a patient with a previous cranioplasty. *Spine* 26(19), E463-E467

Parahoo K (2006) *Nursing research: Principles, Process and Issues*. 2nd Edition Palgrave Macmillan, Hampshire

Pathways through participation (2009) *Briefing paper no. 3. Who participates - The actors of participation*. Available at: www.pathwaysthroughparticipation.org.uk/wpcontent/uploads/2009/09/Briefing-paper-3-Who-participates1.pdf

Patterson MM (2005) Multicentre pin care study. *Orthopaedic Nursing* 24(5), 349-60

Patterson M (2006) Impact of external fixation on adolescents: An integrative research review. *Orthopaedic Nursing* 25(5), 300-308

Patterson M (2010) Adolescent experience with traumatic injury and orthopaedic external fixation: Forever changed. *Orthopaedic Nursing* 29(3), 183-192

Pickard JD, Richards HK, and Seeley HM (2015) Impact of antibiotic-impregnated catheters on the reduction in operations for cerebrospinal fluid shunt infection since 1995: evidence from the UK Shunt Registry. *Fluids and Barriers of the CNS*, 12(Suppl 1), O9.

Pieske O, Geleng P, Zaspel J and Piltz S (2008) Titanium alloy pins versus stainless steel pins in external fixation at the wrist: A randomized prospective study. Journal of Trauma and Acute Care Surgery 64(5),1275-1280

Pieske O, Kaltenhauser F, Pichlmaier L, Schramm N, Trentzsch H, Löffler T, Greiner A and Piltz S (2010) Clinical benefit of hydroxyapatite-coated pins compared with stainless steel pins in external fixation at the wrist: A randomised prospective study. *Injury* 41(10), 1031-1036

Pitts B, Hamilton MA, Zelver N and Stewart PS (2003) A microtiter-plate screening method for biofilm disinfection and removal. *Journal of Microbiological Methods* 54(2), 269-276

Pizà G, Caja V, González-Viejo MA and Navarro A (2004) Hydroxyapatite-coated external-fixation pins. *Journal of Bone and Joint Surgery* 86B(6), 892-897

Placzek R, Ruffer M, Deuretzbacher G, Heijens E and Meiss A (2006) The fixation strength of hydroxyapatite-coated Schanz screws and standard stainless steel Schanz screws in lower extremity lengthening. *Archives of Orthopaedic and Trauma Surgery 126*(6), 369-373

Pommer A, Muhir G and Dávid A (2002) Hydroxyapatite-coated Schanz pins in external fixators used for distraction osteogenesis: A Randomized controlled trial. *Journal of Bone and Joint Surgery* 84A(7), 1162-1166

Porter RS and Kaplan JL (Editors) (2013) *MERCK MANUAL* http://www.merckmanuals.com/professional/infectious_diseases/bacteria_and_antibacterial_drugs/lincosamides_oxazolidinones_and_streptogramins.html?qt=&sc=&alt=

Prabhakara R, Harro J, Leid J, Keegan A, Prior M and Shirtliff M (2011) Suppression of the inflammatory immune response prevents the development of chronic biofilm infection due to methicillin-resistant Staphylococcus aureus. *Infection and Immunity* 79(12), 5010-5018

Prabhu K, Rao S, and Rao V (2011) Inducible clindamycin resistance in staphylococcus aureus isolated from clinical samples. *Journal of Laboratory Physicians* 3(1), 25-27

Pratt R, Pellow C, Wilson J, Loveday H, Harper P, Jones S, McDougall C, and Wilcox M (2007) epic2: national evidence based guidelines for preventing healthcare-associated infections in NHS Hospitals in England, *Journal of Hospital Infection*, 65, S1-S59

Price JS, Tencer T, Arm DM and Bohach GA (1996) Controlled release of antibiotics from coated orthopaedic implants. Journal of Biomedical Materials Research 30(3), 281-286

Pocock SJ (1983) *Clinical trials: A practical approach.* Chichester. Wiley

Qi X, Gao J, Sun D, Liang W, Wan Y, Li C, Xu X and Gao T (2008) Biofilm formation of the pathogens of fatal bacterial granuloma after trauma. *Scandinavian Journal of Infectious Diseases* 40(3), 221–228

Qu H, Knabe C, Radin S, Garino J, Ducheyne P (2015) Percutaneous external fixator pins with bactericidal micron-thin sol-gel films for the prevention of pin tract infection. *Biomaterials* 62, 95-105

Raffa G, Marseglia, L, Gitto E and Germanò A (2015) Antibiotic-impregnated catheters reduce ventriculoperitoneal shunt infection rate in high-risk newborns and infants. *Child's Nervous System* 31(7), 1129-1138

Ramage G, Tunney MM, Patrick S, Gorman SP and Nixon JR (2003) Formation of Propionibacterium acnes biofilms on orthopaedic biomaterials and their susceptibility to antimicrobials. *Biomaterials* 24(19), 3221-3227

Reay N (2010) How to measure patient experience and outcomes to demonstrate quality in care. *Nursing Times* 106(7), 12-14

Reichmann DE. And Greenburg JA. (2009) Reducing surgical site infections: A review. *Reviews in Obstetrics and Gynaecology* 2(4), 212-221

Reitz OE and Anderson MA (2013) Comparison of survey methods in studies of the nurse workforce. *Nurse Researcher* 20(4), 22-27

Ribeiro M, Monteiro FJ and Ferraz MP (2012) Infection of orthopaedic implants with emphasis on bacterial adhesion process and techniques used in studying bacterial-material interactions. *Biomaterials* 2(4), 176-194

Richard HM, Nguyen DC, Birch JG, Roland SD, Samchukov MK (2015) Clinical implications of psychosocial factors on pediatric external fixation treatment and recommendations. *Clinical Orthopaedics and Related Research* 473(10), 3154-3162

Rizvi, M., Khan, F., Raza, A., Shukla, I., & bin Sabir, A (2011) Emergence of coryneforms in osteomyelitis and orthopaedic surgical site infections. *The Australasian Medical Journal* 4(7), 412

Robson MC (1979) Infection in the surgical patient: an imbalance in the normal equilibrium. *Clinics in Plastic Surgery* 6(4), 493-503

Rodrigues JN, Zhang W, Scammell BE, and Davis TRC (2014) What patients want from the treatment of Dupuytren's disease—is the Unité Rhumatologique des Affections de la Main (URAM) scale relevant? *Journal of Hand Surgery* (European Volume) 40(2), 150-154

Rogers LC, Bevilacqua NJ, Frykberg RG and Armstrong DG (2007) Predictors of postoperative complication of Ilizarov external ring fixators in the foot and ankle. *Journal of Foot and Ankle Surgery* 46(5), 372-375

Russell A. (2004) Whither triclosan? *Journal of Antimicrobial Chemotherapy* 53(5), 693-695

Ryan SP, and Pugliano V (2014) Controversies in Initial management of open fractures. *Scandinavian Journal of Surgery* 103(2), 132-137

Saleh M and Scott BW (1992) Pitfalls and complications in leg lengthening: the Sheffield experience. *Seminars in Orthopaedics* 7(3), 207–222

Santy J and Newton-Triggs L (2006) A survey of current practice in skeletal pin site management. *Journal of Orthopaedic Nursing* 10(4), 198-205

Santy J (2010) A review of pin site wound infection assessment criteria. *International Journal of Orthopaedic and Trauma Nursing* 14(3), 125-131

Santy-Tomlinson J, Vincent M, Glossop N, Jomeen J, Pearcey P (2011) Calm, irritated or infected? The experience of the inflammatory states and symptoms of pin site infection and irritation during external fixation: A grounded theory study. *Journal of Clinical Nursing* 20(21-22), 3163-3173

Sato W, Ohnishi I, Nishimura N, Nakase, T, Tsuchiya H, Hirose M, Matsushita T, Hirasawa Y and Nakamura K (2003) Correction of tibial deformity in adults. *Journal of Orthopaedic Science* 8(3), 306-312

Schalamon J, Petnehazy T, Ainiedhofer H, Zwick EB, Singer G and Hoellwarth ME (2007) Pin tract infection with external fixation of paediatric fractures. Journal of Paediatric Surgry 42(9), 1584-1587

Schroeder KM, Jacobs RA, Guite C, Gassner K, Anderson B, Donnelly MJ (2012) Use of chlorhexidine-impregnated patch does not decrease the incidence of bacterial colonization of femoral nerve catheters: a randomised control trial. *Canadian Journal of Anaesthesia* 59(10), 950-957

Schweinberger MH and Roukis TS (2008) The effectiveness of Physician-directed external fixation pin site care in preventing infection in a high risk population. *Foot & Ankle Specialist* 1(4), 218-221

Sciubba, D. M., Stuart, R. M., McGirt, M. J., Woodworth, G. F., Samdani, A., Carson, B., & Jallo, G. I. (2005). Effect of antibiotic-impregnated shunt catheters in decreasing the incidence of shunt infection in the treatment of hydrocephalus. Journal of Neurosurgery: Paediatrics, 103(2), 131-136

Sealed Enveloped Ltd (2012) Power calculator for binary outcome superiority trial https://www.sealedenvelope.com/power/binary-superiority

Sheehan K and McMillanS (1999) Response variation in email surveys: and exploration. *Journal of Advertisement Research* 39(4), 45-54

Shimazaki T, Miyamoto H, Andro Y, Noda I, Yonekura Y, Kawano S, Miyazaki M, Mawatari M and Hotokebuchi T (2010) In vivo antibacterial and silver-releasing properties of novel thermal sprayed silver-containing hydroxyapatite coating. *Journal of Biomedical Materials Research Part B Applied Biomaterials* 92B(2), 386-389

Shirai T, Tsuchiya H, Shimizu T, Ohtani K, Zen Y and Tomita K (2009) Prevention of pin tract infections with titanium-copper alloys. Journal of Biomedical Materials Research Part B: Applied Biomaterials 91B(1), 373-380.

Sims M and Saleh M (2000) External fixation – the incidence of pin site infection: a prospective audit. *Journal of Orthopaedic Nursing* 4(2), 59-63

Singh KV, Weinstock GM and Murray BE (2002) An enterococcus faecalis ABC homologue (LSA) is required for the resistance of this species to clindamycin and quinupristin-dalfopristin. *Antimicrobial Agents Chemotherapy* 46(6), 1845-1850

Singh A, Tetreault L, Casey A, Laing R, Statham P, Fehlings M (2015) A summary of assessment tools for patients suffering from cervical spondylotic myelopathy: A systematic review on validity, reliability and responsiveness. *European Spine Journal* 24 (Supplement 2); S209-228

Smith TJ, Galm A, Chatterjee S, Wells R, Pedersen S, Parizi M, Goodship AE and Blunn GW (2006) Modulation of the soft tissue reactions to percutaneous orthopaedic implants. *Journal of Orthopaedic Research* 24(7), 1377-1383

Speigelberg B, Parrett T, Dheerendra SK, Khan WS, Jennings R and Marsh DR (2010) Ilizarov principles of deformity correction. *Annals of the Royal College of Surgeons England* 92(2), 101-105

Stepanović S, Voković D, Dakić I, Savić B, and Švabić-Vlahović M (2000) A modified microtitrer-plate test for quantification of staphylococcal biofilm formation. *Journal of Microbiological Methods* 40(2) 175-179

Stevens DL, Aldape MJ, and Bryant AE (2012) Life-threatening clostridial infections. *Anaerobe* 18(2), 254-259

Stiger M, de Goot K and Layrolle P (2002) Incorporation of tobramycin into biomimetic hydroxyapatite coating on titanium. *Biomaterials* 23(20), 4143-4153

Storm-Versloot MN, Vos CG, Ubbink DT and Vermeulen H (2010) Topical silver for preventing wound infection. *The Cochrane Library*

Suller MTE and Russell AD (2000) Triclosan and antibiotic resistance in staphylococcus aureus. *Journal of Antimicrobial Chemotherapy* 46(1),11-18

Tamma PD, Cosgrove SE and Maragakis LL (2012) Combination therapy for treatment of infections with gram-negative bacteria. *Clinical Microbiology Reviews* 25(3), 450-470

Tande AJ, & Patel R. (2014) Prosthetic joint infection. *Clinical Microbiology Reviews* 27(2), 302-345

Traub WH & Leonhard B. (1995) Heat stability of the antimicrobial activity of sixty-two antibacterial agents. Journal of Antimicrobial Chemotherapy 35(1), 149-154

Thiryayi W, Naqui Z and Khan S (2010) Use of Taylor Spatial frame in compression arthrodesis of the Ankle: A Study of 10 cases. *Journal of Foot & Ankle Surgery* 49(2), 182-187

Tiemann AH and Hofmann GO (2009) Principles of the therapy of bone infections in adult extremities: Are there any new developments? *Strategies in Trauma Limb Reconstruction* 4(2):57-63

Timms A, Vincent M, Santy-Tomplinson J, Hertz K (2011) Guidance on pin site care. *Royal College of Nursing*, London

Torgerson D and Torgerson C (2008) *Designing randomised trials in health education and the social sciences*. Palgrave Macmillan, New York.

Treadwell JR (2005) Rail external fixation for stabilization of closing base wedge osteotomies and lapidus procedures: A retrospective analysis of sixteen cases. *Journal of Foot & Ankle Surgery* 44(6), 429-436

Van Middendorp JJ, Slooff W-BM, Nellestein R and Öner FC (2009) Incidence of and risk factors for complications associated with halo-vest immobilization: A prospective, descriptive cohort study if 239 patients. *Journal of Bone and Joint Surgery* 91A(1), 71-79

Vasiliadis E, Grivas T, Psarakis S. Papavasileiou E, Kaspiris A and Triantafyllopoulos G (2009) Advantages of the Ilizarov external fixation in the management of intra-articular fractures if the distal tibia. *Journal of Orthopaedic Surgery and Research* 4,35 http://www.biomedcentral.com/content/pdf/1749-799X-4-35.pdf

Vickery K, Hu H, Jacombs AS, Bradshaw DA and Deva AK (2013) A review of bacterial biofilms and their role in device-associated infection. *Healthcare Infection* 18(2), 61-66

Voos K, Rosenberg B, Fagrhi M, and Seligson D (1999). Use of a tobramycin-impregnated polymethylmethacrylate pin sleeve for the prevention of pin-tract infection in goats. *Journal of Orthopaedic Trauma* 13(2), 98-101

W-Dahl A, Toksvig-Larsen S and Linstrand A (2003) No difference between daily and weekly pin site care: A randomised study of 50 patients with external fixation. *Acta Orthopaedica* 74(6), 704-708

W-Dahl A and Toksvig-Larsen S (2004) Pin site care in external fixation sodium chloride or chlorhexidine solution as a cleansing agent. *Archives of Orthopaedic and Trauma Surgery* 124(8), 555-558

Walker S, Brett S, McKay A, Lambden S, Vincent C and Sevdalis N (2011) Observational Skill-based Clinical Assessment tool for Resuscitation (OSCAR): development and validation. *Resuscitation* 82(7), 835-844

Walker J (2015) The need for patient reported experience measures. *RCNi* http://rcni.com/newsroom/opinion/need-patient-reported-experience-measures-26266

Waltz CF, Strickland CL and Lens ER (1991) *Measurement in nursing research*. 2nd Edition, Philadelphia, FA Davis.

Wang D and Bakhai A (2006) *Clinical trials: A practical guide to design, analysis and reporting.* Remedica, Spain.

Wang X, Itu A, Sogo Y, Li X and Oyane A (2009) Silicate-apatite composite layers on external fixation rods and in vitro evaluation using fibroblast and osteoblast. *Journal of Biomedical Materials Research Part A* 92(3),1181-1189

Wehrli, W (1983) Rifampin: Mechanisms of action and resistance. *Reviews of Infectious Diseases* 5(3), S407-411

Weichman KE, Clavin NW, Miller HC, McCarthy CM, Pusic AL, Mehrara BJ and Disa JJ (2015) Does the use of biopatch devices at drain sites reduce perioperative infectious complications in patients undergoing immediate tissue expander breast reconstruction? *Plastic and Reconstructive Surgery* 135(1), 9e-17e

Wickens DJ, West G, Kelly PJ, Verran J, Lynch S and Whitehead KA (2012) Antimicrobial activity of nanocomposite zirconium nitride/silver coatings to combat external fixation bone fixation pin infection. *International Journal of Artificial Organs* 35(10), 817-825

Widmer AF, Wiestner A, Frei R and Zimmerli W (1991) Killing of nongrowing and adherent Escherichia coli determines drug efficacy in device related infections. *Antimicrobial Agents and Chemotherapy* 35(4), 741-746

Williams I, Venables WA, Lloyd D, Paul F and Critchley I (1997) The effects of adherence to silicone surfaces on antibiotic surfaces in Staphylococcus aureus. *Microbiology* 143(7), 2407-2413

Wu P and Grainger DW (2006) Drug/device combinations for local drug therapies and infection prophylaxis. *Biomaterials* 27(11), 2450-2467

Wu SC, Crews RT, Zelen C, Wrobel JS and Armstrong DG (2008) Use of chlorhexidine-impregnated patch at pin site to reduce local morbidity: The ChiPPS pilot trial. *International Wound Journal* 5(3), 416-422

Wu Y, Zitelli JP, TenHuisen K, Yu X and Libera MR (2011) Differential response of Staphylococci and osteoblasts to varying titanium surface roughness. *Biomaterials* 32(4), 951-960

Yilmaz G, Aydin K, Iskender S, Caylan R and Koksal I (2007) Detection and prevalence of inducible clindamycin resistance in staphylococci. *Journal of Medical Microbiology* 56(3), 342-5

Yuenyongviwat V and Tangtrakulwanich B (2011) Prevalence of pin site infection: The comparison between silver sulfadiazine and dry dressing among open tibial fracture patients. *Journal of the Medical Association of Thailand* 94(5), 566-569

Zalavras CG, Patzakis P and Holtom P (2004) Local antibiotic therapy in the treatment of open fractures and osteomyelitis. *Clinical Orthopaedic and Related Research* 427; 86-93

Zecconi A and Scali F (2013) Staphylococcus aureus virulence factors in evasion from innate immune defences in human and animal diseases. *Immunology Letters* 150(1), 12-22

Zhao XL and Drlica K (2001) Restricting the selection of antibiotic-resistant mutants: A general strategy derived from fluoroquinolone studies. *Clinical Infectious Diseases* 33(3), S147-S156

Ziberman M and Elsner JJ (2008) Antibiotic-eluting medical devices for various applications. *Journal of Controlled Release* 130(3), 202-215

Zinkernagel AS, Zinkernagel MS, Elzi MV, Genoni M, Gubler J, Zbinden R and Mueller NJ (2008) Significance of Staphylococcus lugdunensis bacteremia: report of 28 cases and review of the literature. *Infection* 36(4), 314-321

Ziran B, Smith W, Angelen J and Tornetta P (2007) External fixation: How to make it work. *Journal of Bone and Joint Surgery* 89A(7), 1620-1632

Appendix 1 – Survey Monkey Questionnaire

The purpose of this survey is to identify the trends and practices of pin site care. Please respond to each question about how you manage pin sites.

If you have any questions or wish to provide any additional feedback please contact Jennie.Walker@nottingham.ac.uk.

The results of this will form part of a PhD thesis and is carried out in conjunction with the University of Nottingham and the Biomaterials Related Infection Group.

Many thanks

Jennie

1. Please tell us about where you work

Please tell us about where you work Trust/Healthcare provider:	
City/Town:	
Country:	

2. Please select which best describes your role.

- ○ Nurse
- ○ Nurse specialist
- ○ Nurse practitioner
- ○ Nurse consultant
- ○ Doctor
- ○ Consultant
- ○ Occupational Therapist
- ○ Orthotist
- ○ Physiotherapist
- ○ Other (please specify)

Please select the option that best describes how you clean pin sites.

3. How often do you clean pin sites?

- More than twice daily
- Twice daily
- Once daily
- Every 2-3 days
- Once weekly
- Less than once weekly
- Do not clean pin sites
- Other (please specify)

4. What do you use to clean pin sites?

- Do not clean pin sites
- Chlorhexidine in alcohol 0.5%
- Chlorhexidine in alcohol 0.2%
- Aqueous chlorhexidine
- Normal Saline
- Water
- Other (please specify)

5. How do you manage crusts and dried exudate around the pin site?

- Crusts/ dried exudate are left in-situ
- Crusts/ dried exudate are removed
- Crusts/ dried exudate are left in-situ, but removed if suspicion or confirmation of infection
- Other (please specify)

Please select the options that best describe your current practices for covering/dressing pin sites.

6. What do you use to dress/cover pin sites?

- ☐ Pin sites are left exposed if clean and dry
- ☐ Biopatch (or similar)
- ☐ Gauze soaked in chlorhexidine
- ☐ Dry gauze
- ☐ Foam dressings (e.g. Allevyn)
- ☐ Figure of 8 bandages
- ☐ Other (please specify)

7. When is the surgical dressing taken down?

- ○ Between 1 and 3 days post-operatively
- ○ Between 3 and 7 days
- ○ At 7 days
- ○ Other (please specify)

Please select the options that best describe your practices regarding application of compression around pin sites.

8. Do you apply compression around the pin sites?

- ○ Compression is applied to pin sites for the length of treatment
- ○ Compression is applied in the immediate post-operative period only
- ○ Compression is applied for up to 48 hours post-operatively
- ○ Compression is not applied
- ○ Other (please specify)

9. If compression is applied to pin sites, please state which devices are used.

☐ If compression is applied to pin sites, please state which devices are used. Manufactured Clips

☐ Manufactured Bungs

☐ Bungs made from 20 ml syringes

☐ Bungs made from Foley catheters

☐ Other (please specify)

10. Do you allow patients with external fixators to bath or shower? Please select 2 answers.

☐ Do you allow patients with external fixators to bath or shower? Please select 2 answers. Bathing is permitted

☐ Bathing is not permitted

☐ Showering is permitted

☐ Showering is not permitted

Comments

Thank you for taking time to complete this questionnaire. Your responses are greatly appreciated.

If you have any comments or would like any further information please contact Jennie.Walker@nottingham.ac.uk.

Appendix 2 – Antibiogram sheet

		Interpretation of zone diameter (mm)				
Ciprofloxacin	Cip		R≤ 17 S≥ 18	4 0		
Teicoplanin	Tec		R≤ 14 S≥ 15	1 0		
Fusidic Acid	Fd		R≤ 29 S≥ 30	2 0		
Vancomycin	Va		R≤ 11 S≥ 12	4 0		
Rifampicin	Rd		R≤ 29 S≥ 30	1 0		
Clindamycin	Da		R≤ 25 S≥ 26	2 0		
Gentamicin	Cn		R≤ 19 S≥ 20	4 0		
Trimethroprim	W		R≤ 19 S≥ 20	1 0		
Methicillin	M		R≤ 14 S≥ 15	2 0		
Erythromycin	E		R≤ 19 S≥ 20	4 0		
Cloramphenicol	C		R≤ 14 S≥ 15	1 0		
Tetracycline	Te		R≤ 19 S≥ 20	2 0		
Penicillin	P		R≤ 25 S≥ 25	4 0		

Appendix 3 - SOP for collar manufacture

Division of Orthopaedic Trauma and Sports Medicine
Laboratory Protocol

Title: Impregnation of silicone collars with antimicrobial agents

Summary

The procedure described below is to be used when impregnating silicone discs with antimicrobial agents. This procedure should be performed using a technique designed to avoid chemical contamination.

Safety

Lab coat, gloves, safety glasses must be worn throughout the procedure. The procedure must be carried out using the extractor hood.

Requirements
Apparatus

250mL beaker
100mL measuring cylinder
Forceps
Fume cupboard
Silicone sheet - 3mm Thickness SI303300
Aluminium

Reagents

Ethanol	Medical School Stores LHM012UE
Chloroform	Medical School Stores LHU0067I
Clindamycin hydrochloride	Sigma C5269
Rifampicin	Sigma R3501
Triclosan	Ciba IRGASAN® DP 300

Method

1) Use designated equipment for the procedure (measuring cylinder, beaker and aluminium sheets).
2) Measure 100mL chloroform in a beaker
3) Add 0.2g clindamycin hydrochloride to the chloroform and allow to dissolve. Chloroform may need to be heated to 40°C to dissolve clindamycin hydrochloride.
4) Once the clindamycin has been dissolved, add 0.2g rifampicin to the solution, followed by 1g triclosan allowing agents to dissolve.
5) Add silicone materials for impregnation to the conical flask and leave for 1 hour.
6) Remove impregnated materials from the flask with forceps. Place on aluminium foil sheets and leave overnight for the chloroform to evaporate.
7) Rinse silicone materials in ethanol and leave to dry for a further 2-3 hours.
8) Place in an autoclave bag ready for sterilisation.

Appendix 4 - Service user evaluation of prototype collars

	Yes	No	Do not know
Would you like to use the product? Free comments:			
Would it be easy to use? Free comments:			
Is it fiddly? Free comments:			
Is it itchy? Free comments:			
Is it uncomfortable? Free comments:			
Is it irritating? Free comments			
Is it likely to fall off? Free comments:			
Is it likely to get in the way? Free comments:			
Would you be willing to join a research study to trial this product? Free comments:			
Is the fact that this is removable/replaceable appealing? Free comments:			
Is the fact that it is washable appealing? Free comments:			
What do you like about the collar?			
What do you dislike about the collar?			
What would you change?			
How easy would this be to use/replace?			

Appendix 5 – Patient information sheet

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham

Participant Information Sheet
(Final version 1.0:26th April 2012)

A pilot study to determine the effectiveness of a novel antibiotic impregnated collar in preventing external fixator pin site infection

Name of Researcher(s): Professor B. Scammell, Dr R. Bayston, Mrs J Walker

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Please ask us if there is anything that is not clear.

What is the purpose of the study?
The purpose of this study is to test a new method to prevent infection occurring at the pin site (where your pins enter the skin). The study will compare two types of pin site dressing designed to reduce infection, against the way we currently care for pin sites.

This study is being conducted as part of a research degree in conjunction with the University of Nottingham and Mrs Jennie Walker.

Why have I been invited?
You are being invited to take part because your Consultant has decided that your injury will need to be treated with an external fixator or halo brace. We are inviting fifty participants like you to take part in the study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do 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. This would not affect your legal rights or medical care.

What will happen to me if I take part?
You will not have to do anything different to what you would normally have to do to care for your halo or external fixator.

If you agree to join the study you will be randomly allocated to one of the two study groups. Group 1 will receive normal care of pin sites as instructed by the doctors and nurses. Group 2 will be treated with collars around each pin which contain antibiotics. You have equal chances of being allocated to either group. The researcher will come and see you while you are attending the hospital to see your consultant about your external fixator or halo brace. You will not be required to come back to the hospital in between your scheduled visits, or once you have had your fixator removed. The researcher will spend approximately 15 minutes talking to you at each appointment about your pin sites and looking at them to see if there are any signs of infection. If one of your pins becomes infected the researcher will take a swab (sample) of the infection to test in the laboratory. The researcher will also ask you about any problems that you may have had with your pins or the collars since your last visit, and check your medical records to see what other medicines you have been prescribed. The study will finish when the consultant removes the external fixator.

At the end of the study you will be asked to complete a short questionnaire. If you have difficulty completing the questionnaire or would like help with this the researcher will be able to help you complete the form. The researcher will look at your medical notes six months after you have had your fixator removed to check that you have not experienced any further problems.

Expenses and payments
Participants will not be paid to participate in the study.

What are the possible disadvantages and risks of taking part?
As some of the collars will contain antibiotics there is a small risk of local reaction to the collar. This technology has been shown to be effective in catheters used to treat hydrocephalus (water on the brain) and catheters used for dialysis without any hypersensitivity or toxicity problems. The antibiotics used in the collars are not a new type of antibiotics, and therefore we do not expect to experience such problems.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study will help provide important information for the future about preventing pin site infection in patients with external fixators or halo braces.

What happens when the research study stops?

Your involvement in the study will end once you have your pins removed. The use of the collars will not be available after the study finishes if you require further treatment with an external fixator.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Jennie Walker if you have any problems or concerns regarding the study. Contact details are at the end of this information leaflet. If you remain unhappy and wish to complain formally, you can do this by contacting NHS Complaints. Details can be obtained from your hospital.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it. All handling, processing, storage and destruction of data will meet the requirements of the Data Protection Act 1998.

Your personal data (address, telephone number) will be kept for 6 months after the end of the study so that we are able to contact you about the findings of the study (unless you advise us that you do not wish to be contacted). All research data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?
Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)
With your permission your General Practitioner (GP) will be informed that you are involved with the study. Only information about the study will be given to your GP, not the information obtained by the researcher.

What will happen to any samples I give?
Any swabs or samples that are taken by the researcher from infected pin sites will be recorded. Bacteria identified from your pin sites will be frozen within the laboratory for further use if required.

What will happen to the results of the research study?
At the end of the study, if you wish, the researcher will write to you and inform you of the results of the study. The results of the study will be published in the medical and healthcare press. You will not be identified in any of the material published.

The results from this study will also be written up as part of a PhD study.

Who is organising and funding the research?
This research is being organised by the University of Nottingham and is being funded by Arthritis Research UK.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Nottingham Research Ethics Committee.

Further information and contact details
Jennie Walker
Academic Division of Orthopaedic and Accident Surgery,
C floor, West Block
Queen's Medical Centre
Nottingham
NG7 2UH

Telephone: (0115) 9249924 ext: 64170
Email: Jennie.Walker@nottingham.ac.uk

Appendix 6 – Participant consent form

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham

CONSENT FORM
(Final version 1.0:8th March 2012)

Title of Study: A pilot study to determine the effectiveness of a novel antibiotic impregnated collar in preventing external fixator pin site infection

Name of Researcher: Jennie Walker

Name of Participant:

Please initial

1. I confirm that I have read and understand the information sheet version number ……dated..... for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand and agree that local swab samples will be taken for analysis of bacteria. ☐

5. I agree to my GP being informed of my participation in this study. ☐

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

7. I would like to be informed of the study results at the end on the trial ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from Principal Investigator)	Date	Signature
_____	_____	_____
Name of Principal Investigator	Date	Signature

Appendix 7 – UoN Sponsor permission

The University of Nottingham

Our reference:
RGS 12009
Your reference:
12/EM/0138

0115 9515679
paul.cartledge@nottingham.ac.uk

Nottingham 2 REC
East Midlands REC centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Research and Graduate Services
University of Nottingham
King's Meadow Campus
Lenton Lane Nottingham
NG7 2NR

Dr Roger Bayston, Chief Investigator
Assoc Professor / Reader, Surgical Infection
Academic Division of Orthopaedic & Accident Surgery
School of Clinical Sciences,
C floor, West Block, Queens Medical Centre.
Nottingham, NG7 2UH.

15th March 2012

Dear Sir or Madam,

Sponsorship Statement

Re: A pilot study to determine the effectiveness of a novel antimicrobial collar in preventing external fixator pin site infection

I can confirm that this research proposal has been discussed with the Chief Investigator and agreement to sponsor the research is in place.

An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*

Any necessary indemnity or insurance arrangements will be in place before this research starts. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Yours faithfully

Paul Cartledge
Head of Research Grants and Contracts
University of Nottingham

world-changing research

Appendix 8– NUH R&I permission

Nottingham University Hospitals NHS
NHS Trust

research & innovation

Research & Innovation
Nottingham Integrated Clinical Research Centre
C Floor, South Block
Queen's Medical Centre Campus
Derby Road, Nottingham NG7 2UH
Direct Dial: 0115 849 3320
R&I Dept: 0115 970 9049
Tel: 0115 924 9924
Fax: 0115 849 3295
www.nuh.nhs.uk
nuhrise.org

12 JUL 2012

Ms Jennie A Walker
Post Research Fellow
Division of Orthopaedic and Accident Surgery,
School of Clinical Sciences
Nottingham University Hospitals
Queens Medical Centre Campus
Nottingham
NG7 2UH

Dear Ms Walker

Re: 12ID011
CSP# 83477
Prevention of pin site infection: A pilot study

The R&I Department has considered the following documents:

REC favourable opinion with conditions 25/04/2012
REC favourable opinion conditions met 02/05/2012
Protocol version 1.0 08/03/2012
GP information sheet version 1.0 08/03/2012
Participant consent form version 1.0 08/03/2012
Participant information sheet version 1.0 26/04/2012
Questionnaire: Health and wellbeing 08/03/2012

Your study now has R&I approval, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

We are here for you

That you:

1. Comply with all relevant laws, regulations and codes of practice applicable to the trial including but not limited to, the UK Clinical Trials Regulations, Medicines for Human Use (Clinical Trial) Regulations 2004, principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version), the Human Rights Act 1998, the Data Protection Act 1998 the Medicines Act 1968, the NHS Research Governance Framework for Health and Social Care (version 2 April 2005). Should any of these be revised and reissued the latest version of the relevant laws and regulations will apply. Copies of the regulations are available from the R&I Office or via the R&I website http://nuhrise.org

2. For NUH sponsored studies ;

   - Accept the responsibilities as outlined in the "Clinical Trial Delegation of Sponsorship responsibilities to Chief Investigator" agreement.
   - Request R&I review of any proposed amendments or changes to study documentation prior to submission to the regulatory authorities by submitting documents to rdappl@nuh.nhs.
     *Submissions may not be made to REC and MHRA (as appropriate) without NUH sponsor authorisation.

3. For studies ***not*** sponsored by NUH request written approval from the R&I department, Ethics Committee and MHRA (as appropriate) for any Protocol Amendments, changes to study documentation or changes to study team.

   For studies adopted onto the NIHR portfolio please submit documents to NUHNT.TRENTCLRN@nhs.net

   For all other studies please use rdamend@nuh.nhs.uk

4. Ensure all study personnel, not employed by the Nottingham University Hospitals NHS Trust hold either honorary contracts/letters of access with this Trust, before they have access to any patients or staff, their data, tissue or organs or any NUH facilities.

5. According to R&D SOP 11 - "Adverse Event Monitoring, Recording and Reporting for investigators" report

any Serious Adverse Events to the R&D department. For NUH sponsored studies, report any Serious Adverse Events to the R&I department according to R&I SOP 11 - "Adverse Event Monitoring, Recording and Reporting for investigators

6. According to R&D SOP 12 - "Protocol Violations and Serious Breach Reporting" report any Serious Breach of the UK Clinical Trial regulations in connection with the trial or Serious Breach of the protocol, immediately after becoming aware of the breach to R&I.

7. Complete Annual Safety, Progress reports and End of Study reports as required by R&I, Ethics Committee and the MHRA.

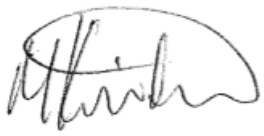
8. Notify R&I within 7 calendar days of the first participant recruited onto the study, as well as the detail of the specific recruitment date. Please email the recruitment notification to rdmon@nuh.nhs.uk

9. For GTAC-approved studies, the R&D approval letter should be forwarded to GTAC via the sponsor. GTAC should then issue a site authorisation letter which must be received by each site prior to recruitment commencing. A copy of this letter must be forwarded to R&I.

This approval letter constitutes a favourable Site Specific Assessment (SSA) for this site.

Please note that the R&D department has a database containing study related information, and personal information about individual investigators e.g. name, address, contact details etc. This information will be managed according to the principles established in the Data Protection Act.

Yours sincerely,



Dr Brian Thomson / Dr Maria Koufali
Director of R&D / Deputy Director Research and Innovation

cc Nottingham Research Ethics Committee

Appendix 9 – Research ethics approval

NRES Committee East Midlands - Nottingham 2
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839437
Facsimile: 0115 8839294
02 May 2012

Ms Jennie A Walker,
Division of Orthopaedic and Accident Surgery,
C Floor, West Block,
Queens Medical Centre,
Nottingham.
NG7 2UH

Dear Ms Walker

Full title of study:	A pilot study to determine the effectiveness of a novel antimicrobial collar in preventing external fixator pin site infection
REC reference number:	12/EM/0138

Thank you for your e-mail of 26th April 2012. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 23 April 2012. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

Document	*Version*	*Date*	
Evidence of insurance or indemnity		24 April 2012	
Participant Information Sheet	1.0	26 April 2009	

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

12/EM/0138	Please quote this number on all correspondence

Yours sincerely

Stephen Briggs
Assistant Co-ordinator

E-mail: stephen.briggs@nnotts.nhs.uk

Copy to: *Chief Investigator - Dr Roger Bayston, Associate Professor / Reader, Surgical Infection, University of Nottingham, Division of Orthopaedic and Accident Surgery, C Floor, West Block, Queens Medical Centre, Nottingham. NG7 2UH*

R & D - Ms Charlotte Davies, Nottingham University Hospitals, Research and Innovation, C floor South Block, Queens Medical Centre Campus, Derby road, Nottingham. NG7 2UH.

Sponsor – Mr Paul Cartledge, University of Nottingham, Research Innovation Services, Kings Meadow Campus, Lenton Lane, Nottingham. NG7 2NR

Appendix 10 - Study protocol

This is the study protocol approved by Nottingham University (Sponsor), the local Research Ethics Committee and Nottingham University Hospital's Research and Innovation department (March-May 2012).

DETAILS OF INVESTIGATIONAL MEDICAL DEVICE

Device Description

The novel collar will be made from medical grade silicone with a hole in the centre where the pin will sit and a slit through one side of the collar to allow placement and removal of collar. The active silicone collar will be impregnated with antimicrobials and is designed to reduce infection around pin sites. All the antimicrobials in the study have been used topically or systemically and allergic reactions have been very uncommon.

The novel collar will be manufactured within the Division of Orthopaedic and Accident Surgery by the researcher. The product will not be CE marked. The device will be applied to newly inserted pins which are part of external fixator devices to determine effectiveness in preventing PSI over the duration of external fixation.

Contraindications for the use of this device include allergy to silicone or the antimicrobials used within the device.

Packaging and labelling

Each novel silicone collar device will be autoclaved and sealed in packaging which will be labelled identifying the name of the study and the principle researcher.

Storage, supply and return

Silicone collars are to be stored at room temperature in a designated area within the Academic Division of Orthopaedic and Accident Surgery.

Known Device Effects

Not known for novel antimicrobial collar.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

Research Question: Can antimicrobial collars designed to minimise bacterial resistance prevent or reduce PSI?

Hypothesis: The use of an antimicrobial collar applied to pin sites of external fixator devices will prevent pin site infection.

This research will form part of a PhD course.
PRIMARY OBJECTIVE
To determine if the use of an antimicrobial collar applied to pin sites of external fixator devices will prevent the occurrence of pin site infection.

SECONDARY OBJECTIVES
Identify which bacteria are commonly associated with pin site infection.
Determine whether antimicrobial collars reduce or prevent PSI
To Identify which is the most effective method (of those studied) in preventing PSI
Determine whether the intervention (if successful) is cost-effective

TRIAL / STUDY DESIGN
The study will be a single centre randomised controlled trial, taking place within the NUH NHS Trust and managed by a single trial management group based within the Academic Division of Orthopaedic and Accident Surgery. This is a study of a one-off medical device intended at this stage only for use within Nottingham University Hospitals.

Primary endpoint
The Primary endpoint of this study is when the participant has the external fixator removed. Time of removal will be determined by the consultant managing clinical treatment the participant.

Primary outcome measures:
Number of patients with infected pin sites
Number of infected pins

Secondary endpoint
Secondary outcomes include:
Adverse reactions to collars
Health care utilisation and additional treatments such as oral antibiotics, readmission, early removal of fixators, osteomyelitis will be recorded
Severity of infections observed;
Cost analysis if the collars are effective.

Safety endpoints
Time until pin sites become infected will be noted for all patients within the study. Other safety endpoints will include adverse events (AEs) relating to the use of the collars. If there is significant local reaction to the novel collar the devices will be removed and continue to be treated as directed by the clinical care team.

Participants treated with the novel collar may receive oral or intravenous antibiotic therapy to treat any occurring pin site infection. If it is thought that persistent infection may result from the novel collar use, the devices will be removed and participants continue to receive pin site care as directed by the clinical care team.

Stopping rules and discontinuation
The research will be halted if new data or information comes to light during the study that would indicate that the proposed study should discontinue. Participants will be informed verbally and by written communication in this event.

Should the research participant wish to withdraw from the study at any point they should inform the researcher of the wish to withdraw from the study. This will be recorded in writing and will not affect the participant's on-going clinical treatment. Once the research participant has withdrawn from the trial they will not be permitted to rejoin the study if they later change their mind.

If clear evidence that the novel collars are ineffective in preventing infection before the end of the trial, the device may be discontinued.

RANDOMIZATION AND BLINDING
Participants will be randomly allocated to either novel silicone collar, or control study groups. Randomisation will be carried out by the clinical trials unit using block randomisation method using blocks of 5 to ensure equal numbers are allocated to each study group.

TRIAL MANAGEMENT
The day-to-day management of the study will be co-ordinated through Jennie Walker. The research will be monitored and supervised by Academic supervisors and the Academic Institution. The conduct of the research will be monitored by the Chief Investigator of the study. Monthly meetings will be scheduled with the study team to enhance coordination. This will include a progress report and reporting of any problems as well as a time-line report.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT
The trial will last from March 2012 to July 2015.

Participants will be involved with the study for the duration of time spent within the external fixator or halo immobilisation (i.e. from when the external fixator is applied to when it is removed). Follow-up by the investigator and assessment of PSI will discontinue once the participant has the fixator removed. This time will be dictated by the Consultant managing the participant's clinical condition. Duration of fixation is expected to be approximately 12 months for lower limb reconstruction

with external fixation and approximately 3 months for halo immobilisation. Medical notes will be reviewed 6 months following removal of fixator to identify any late complications.

Participants will be assessed at each outpatient appointment. The frequency of outpatient appointments will be directed by the Consultant managing the clinical condition. It is predicted that these appointments will be at two weekly intervals. At each appointment the Investigator will inspect the pin sites and enquire about any problems experienced and the use of antimicrobial therapy (i.e. oral antibiotics or lotions). The medical team will remain responsible for managing PSI in both study groups.

End of the Trial
Follow up and assessment will conclude once the external fixation device has been removed. The end of the Trial will therefore be when the last remaining participant has the external fixation device removed.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment
Potential participants will be identified by the clinical care team. If the participant is in agreement the researcher will speak to the individual during the clinic visit or whilst the participant is on the ward. If it is not possible to speak to potential participants prior to fixation application the investigator will make contact within 72 hours of having an external fixator placed. The nature of the study will be explained and appropriate written information will be left with the individual if they would like further information on the study. The investigator will return at a mutually agreed time to answer any questions and discuss the project.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant of all aspects pertaining to participation in the study.
If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages. It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Inclusion criteria

- Over 18 years of age.
- Has the mental capacity to provide informed consent for participation within the study.
- Has either fracture or pathology of the tibia requiring external fixation, lower limb reconstruction using external fixation or cervical spine pathology requiring halo immobilisation respectively.
- Able to read the research literature and understand verbal information regarding the study

Exclusion criteria

- Allergy to the antimicrobials used within the devices.
- Previous medical history of osteomyelitis at the site of pin placement.
- Pregnancy – women who are pregnant or expect to become pregnant during the study period.
- Participants taking long-term antibiotics.
- Participation in other clinical trials involving a medicinal product (CTIMP) drug or device within the last 6 months.
- Unable to understand written or verbal information regarding the study.
- Lacking the mental capacity to give informed consent to participate in the study.
- Current osteomyelitis or systemic infection.

.

Expected duration of participant participation

Study participants will be participating in the study for the duration of time that they are being treated with external fixation/ halo immobilisation. Fixation time is expected to be approximately 12 months for external fixators and 3 months for halo braces.

Removal of participants from therapy or assessments

The research will be halted if new data or information comes to light during the study that would indicate that the proposed study should discontinue. Participants will be informed both verbally and with written communication in this event.

Participants may withdraw from the study at any point. This will be recorded in writing and will not affect the participant's clinical care. Once the participant has withdrawn from the study they are not permitted to rejoin if they later change their mind. If participants wish to withdraw from the trial, permission will be sought to permit follow-up by the investigator at the outpatient appointments scheduled by the clinical care team to collect data regarding PSI. If the participant discovers that they are pregnant during the trial, the participant will be withdrawn from the trail to minimise any risk to the unborn foetus.

Due to the nature of the study and the randomisation process, enrolled participants who are not yet randomised may be replaced, but participants who withdraw after randomisation will not be replaced.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

From the literature and from clinical experience, we expect that the causative bacteria of PSI will be mainly staphylococci, with both *Staphylococcus aureus* and *Staphylococcus epidermidis* represented. We will also encounter some methicillin resistant *Staphylococcus* aureus (MRSA) and potentially *Propionibacterium acnes.* Common causative organisms will be identified with a pre-trial prospective audit in which swabs from infected pin sites will be cultured on conventional media using standard methods. Data from this audit will be used to validate the choice of antimicrobials to be used within the collars. Treatment of pin site infection will remain the responsibility of the clinical team based on results processed by the NHS UKAS accredited laboratory. Serial plate transfer tests (SPTT) will be carried out on audit samples to determine the duration of inhibitory release of antimicrobials and allow for detection of "paradoxical" resistance, where bacteria otherwise inhibited can survive on the surface of the disc due to phenotypic modification (Bayston et al 2009).

Medical Grade silicone will be used to make a series of antimicrobial collars using a pre-determined combination of antimicrobials designed to prevent pin site infection. The choice of antimicrobials are designed to prevent infection occurring at the pin site. Antimicrobial combination will not be altered within the collar in response to infections. The novel collars will be sterilized by autoclaving, shown not to be damaging to antimicrobial activity. The impregnation technique will be as previously published (Bayston et al 1989, Bayston 2007). All antimicrobials which will be used in the study have been used topically or systemically previously and allergic reactions have been uncommon. A copy of the SOP has been included in Appendix I. Any samples from pin site infections required by the clinical care team to identify bacteria and sensitivities will be processed by the NHS pathology laboratory. It will be the results from the NHS pathology laboratories that will inform clinical treatment of pin site infection. Samples obtained by the research team will be for research purposes only and will not influence clinical treatment of pin site infection.

The study will seek to recruit 50 participants with tibial fracture requiring external fixation, undergoing lower limb reconstruction with external fixation or cervical spine pathology requiring halo fixation. Possible participants for this study will be identified by the medical team who will inform the principal investigator (Ms J Walker), who will invite the patient to participate and take informed consent. The CTU will randomize the patient into either the control group or the novel collar group. There will be approximately 25 participants in each study group.

The active study group will have a novel silicone collar applied to each pin site by Ms Walker (an experienced RGN) within 72 hours of the external fixator being applied, before the patient is discharged home. Each external fixator system (i.e. each patient) will be treated with the same treatment regime. A standard cleansing protocol (standard practice within NUH) will be used in which pin sites will be cleansed at least once weekly with chlorhexidine 0.05% solution using an aseptic non-touch technique.

Novel silicone collar group: participants will have pins dressed with the novel silicone collar. The collar will be removed each time for inspection and cleansing of pin sites (at least once weekly); collar cleaned with 0.09% sodium chloride or distilled water and re-applied to the pin sites. If the period of treatment exceeds 12 weeks the silicone collars will be replaced at the 12 week interval.
Control group (Standard care within NHS): pins cleansed in at least once weekly and dressed at the discretion of the clinical care team.

All patients will continue with standard follow up care as directed by the orthopaedic consultant caring for the external fixator device. The duration of the trial will be determined by the length of time required in external fixation. Clinical need rather than the study will determine the intervals for follow-up. Patients are routinely reviewed every two weeks by the normal health care team in the outpatients department. At these visits pin sites will be assessed by the researcher for PSI and patients asked for comments regarding the use of the novel silicone collars, or with standard care. Infected pin sites will be swabbed by the researcher and cultured by the researcher to identify causative bacteria for research analysis and data generation purposes. Any swabs required by the clinical team to inform the management of pin site infection will be sent for analysis in the usual NHS facilities. Results generated from the NHS laboratory will be used to inform clinicians regarding appropriate choices of antibiotic treatment to treat infection, not data gained from research analysis. The orthopaedic consultant will retain responsibility for managing PSI and starting appropriate treatment. If patients are concerned about infection between visits they are advised to contact the fracture clinic and arrange an additional appointment for review. A summary of treatments and assessments are included in Appendix II.

Incidence of PSI will be recorded at each clinic visit and on removal of the fixator. Infection will be monitored using the Santy-Tomlinson Classification, Checketts-Otterburn grading system and Patterson pin site assessment tools as detailed in Appendix II. Details will be recorded relating to problems experienced and treatments used to manage pin site infection (including the use of antibiotic therapy – oral and intravenous) hospital admission or further surgery. Each pin will be treated as a separate number for final analysis although the primary outcome measure will be number of patients with one or more infected pins. The collars will be removed when the external fixator is removed or if the patient wishes to withdraw from the study. Participation in the study will have no effect on the patients' normal clinical care. Data obtained from the pilot study will be utilized to proceed to a full clinical trial of the collars.

The trial will end once the external fixator or halo brace has been removed and no further follow-up visits will be required.

At the end of the trial the participant will be invited to complete the SF36 questionnaire. Participant’s notes will also be reviewed at 6 months following the removal of the fixator to identify any late complications.
Concomitant and Rescue Medications and Treatments
There are no prohibited concomitant treatments before, during or after the trial.
Compliance

Compliance will not be formally assessed within this study as data will be analysed using intention to treat principles. Compliance with the study will refer to the participant keeping the additional devices in place.

Accountability for devices

The investigator, or an approved representative, will ensure that all investigational devices are stored in a secure area, under recommended storage conditions and in accordance with applicable regulatory requirements.

To ensure adequate records, all devices will be accounted for in the case report form (CRF) and device accountability forms. At the end of the clinical trial all unallocated, unused or returned devices will be destroyed or returned to the Academic Division of Orthopaedic and Accident Surgery.

Criteria for terminating trial

The trial will be stopped if an increased number of PSI are observed or if there is allergy or hypersensitivity to the collar or products used within the collar. Major safety concerns, new information or issues with trial conduct may also form the basis for terminating the trial. Unused collar devices will be returned to the Academic Division of Orthopaedic and Accident Surgery for disposal. This will be done by the named researcher.

STATISTICS

Methods

This is a pragmatic pilot study to determine the efficacy of the collars in preventing PSI. Data from this study will be used to do a power calculation for a further clinical trial. Data will be analysed using SPSS statistical software. If patients wish to withdraw from the study before completion of the trail then data will be analysed up until withdrawal (intention to treat analysis). Data will be summarised and analysed using appropriate parametric or non-parametric methods, depending on the distribution of the data. The variance in outcome measures will be explored in order to power a definitive trial at a later date. Analyses are likely to include Chi square, ANOVA, Kaplan-Meier and multifactorial analyses. Data will be analysed based on intention to treat.

Sample size and justification

This is a pragmatic study. Sample size is based on number of patients that will be seen in the clinical setting during the study period. Data from this pilot study will be used to power a definitive trial. The sample size has been determined by the number of patients feasible to recruit within the designated study period based on previous audit and current clinic attendance. 50 participants will be recruited for this study.

Assessment of performance
Participants will be assessed at each outpatient appointment. Follow up will be directed by the Consultant in response to the clinical need. It is predicted that follow up will be at two week intervals. The researcher will assess the participant for PSI using the Santy-Tomlinson classification, Checketts-Otterburn grading system and Patterson pin site assessment tool, and enquire about the use of antimicrobial therapy used other than those advised by the clinical care team. The medical team will remain responsible for managing PSI in both study groups.

Medical notes will be reviewed at 6 months following removal of the fixator to identify any late occurrence of infection or adverse events. Follow-up and assessment of PSI in clinics will discontinue once the participant has the external fixation device removed.

Definition of populations analysed
Data will be analysed using intention to treat principles using

Safety set: All randomised participants who receive the study device
Full Analysis set: All randomised participants who receive the study device and for whom at least one post-baseline assessment of the primary endpoint is available.
Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

ADVERSE EVENTS
Definitions
Adverse Events
An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product/device administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:
1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. Overdose of concurrent medication without any signs or symptoms.

Adverse Device Effects

An adverse device effect is defined as any untoward and unintended response to a medical device and includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of a user error.
Adverse effects from the novel collar may include:
Reddening of skin in contact with the device
Local itching
Infection at the pin site
Local soft tissue reaction where the device has been placed.
All the above adverse effects will be recorded on the case report forms.

Serious Adverse Events

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Serious Adverse Device Effects

A **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that resulted in any of the consequences, characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. Note that this definition captures "near misses" as well as actual incidents.

An **unexpected adverse device effect** is any adverse device effect, the specificity or severity of which is not consistent with the current Investigator's Brochure.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial device which makes a causal relationship incompatible or for which other treatment, drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial device which makes a causal relationship a reasonable possibility, but which could also be explained by other treatments, devices, drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial device which makes a causal relationship a reasonable possibility, and is unlikely to be due to other treatments, devices, drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial device which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study device is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Device Effect.

Recording and Reporting of Adverse Events

All adverse events (AEs) will be recorded as they are reported whether spontaneously volunteered or in response to questioning about well being at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. A note of any concomitant medication will also be made so that a full assessment of the AE can be made.

Abnormal laboratory test results that are deemed clinically significant by the investigator and that lead to a change or temporary or permanent discontinuation in the use of the device, or require intervention or diagnostic evaluation to assess the risk to the subject will be recorded as adverse events or adverse device effects in the CRF and instigate further investigation and follow up as appropriate.

All AEs, SAEs, ADEs and SADEs will be documented in the subject's medical records and CRF. All events must be followed until resolution, or for at least 30 days after discontinuation in use of the device, whichever comes first.

Participants will be asked to contact the study site immediately in the event of any SAEs or SADEs. The Chief Investigator shall be informed immediately of any serious events and shall determine seriousness and relationship in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

All adverse events and adverse device effects will be recorded and reported to the REC as part of the annual reports.

SAEs and SADEs will be reported to the REC as stated below. The Chief Investigator will be responsible for all adverse event reporting.

The Chief Investigator will:

Assess the event for seriousness, expectedness and relatedness to the trial device. Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
If the event is deemed serious, related and/or unanticipated to the trial device, shall inform the REC using the reporting form found on the NRES web page within 15 days of knowledge of the event.
Shall, send any follow-up information and reports to the REC.
Make any amendments as required to the study protocol and inform the REC as required.

Participant removal from the study due to adverse events
Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005, the Medical Device Directive.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Device accountability

Device supplies will be kept in a secure, limited access storage area under the storage conditions specified by manufacturer.

The investigator and the local site staff shall maintain records of the study devices delivery to the site, an inventory at the site, the distribution to each participant, and the return to the storage or alternative disposition of unused study devices. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site staff will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study devices received by the site shall be accounted for.

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.' A copy of the study CRF is included in Appendix III

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents
Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents
The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION
All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY
Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; device accountability, device records and equipment calibration logs.

The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10%) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University Of Nottingham Research Code Of Conduct, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.
Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Results from the study will be published in peer reviewed scientific journals. Participants will not be identified in any publications. Results will also be published on relevant websites and presented at conference. Data gained from this trial will also form part of a PhD thesis.

STUDY FINANCES

This study is funded by Arthritis Research UK.

Participants will not be paid to participate in the trial.

Appendix 11 – Case report forms

Prevention of pin site infection: A feasibility study
Case Report Form Version 1 01/12/2011

Checketts and Otterburn 1993

Grade	Appearance
Minor Infections	
1	Slight redness around the pin together with a little discharge and settles with better pin site care.
2	Redness in the skin, discharge from the pin site and pain and tenderness in the soft tissues. Settles with improved pin site care and a short course of the appropriate antibiotic which is chosen according to the organism cultured. In almost all cases the organism will be *Staphylococcus aureus*.
3	The same as grade 2 but fails to respond with diligent pin site care and the appropriate antibiotic. The affected pin or pins are re-sited and external fixation can be continued.
Major infections	
4	There is severe soft tissue infection involving several pins, sometimes with loosening of the pins. Re-sitting of the pins is impossible and external fixation must be abandoned.
5	There is radiographic evidence of osteomyelitis in addition to soft tissue involvement. External fixation must be abandoned and the infection then resolves.
6	Occurring after fixator removal following completion of the treatment. The pin track heals initially but subsequently, at intervals, will break down and discharge. The infection will clear with curettage of the pin track in the soft tissue and bone. Will usually show sequestra in the bone with reaction in the adjacent periostium on the proximal cortex.

Patterson 2005

Complications: Pin-site reaction								
Date	Redness	Swelling	Discomfort	Loose	Crusting	Skin/pin tent	Drainage	Total
	1-2-3	1-2-3	1-2-3	Y=20 No=0	1-2	Y=1/No=0	1-2-6	
	1-2-3	1-2-3	1-2-3	Y=20 No=0	1-2	Y=1/No=0	1-2-6	
	1-2-3	1-2-3	1-2-3	Y=20 No=0	1-2	Y=1/No=0	1-2-6	

Redness	Swelling	Loose	Tenting
1= mild erythema<0.5cm	1= mild swelling <0.5cm	20= Yes	1= Yes
2= mod erythema 0.5-1.0cm	2= mod swelling 0.5-1.0cm	0 = No	0= No
3= severe erythema >1cm out from pin	3= severe swelling >1cm out from pin		

Discomfort 1= mild w/care intermittent 2= mod guarding against pin care, crisis imminent 3= severe pain reported/observed, combative, constant pain	Crusting 1 = some ½ or less, surface area of the pin 2 = completely encircles the pin
Drainage 1= serous/clear 2= drainage w/colour red, cream, tan, green 6= pus from pin site	6 week check up: Date...../...../..... Req antibiotic....Yes.....Type.....No Req lancing.....Yes.....No Req pin removal.....Yes.....No Change in protocol.....Yes.....No

	Pain	Redness	Discharge	Swelling	General symptoms
Calm	May be painless. Only mild pain. Reduces after application of fixator.	Often none Sometimes a little Not spreading	Sometimes none Sometimes minor	No Swelling	No other issues
Irritated	Mild to moderate. 'Uncomfortable'	Some redness but not spreading. No hot or taut skin	'Weepy' Begins to weep when it has not before/ increased amount of discharge Remains the same consistency and colour as calm Can be persistent in specific pin sites Sometimes bleeding No odour Dressing changes more often	Swelling around pin site only- not spreading	Associated with: Skin movement around the pin Allergy to antiseptic Irritated with physical activity Itchy (owing to reaction/allergy) Dry flaky skin Does not respond to antibiotics May affect all pins sites or just one or two.
Infected	Severe Sudden Increased intensity Throbbing/stinging Joints nearby may be painful Unable to weight-bear Unrelenting on rest Poor response to analgesia.	Deep red Angry looking Spreading Definite boarders Associated with heat	Increased Change in consistency Thick/ more viscous Unpleasant odour (not always) Change in colour Purulent (not always) Dressing changes much more frequent	Localised swelling around affected pin May spread May be severe	Feeling unwell Fever/pyrexia Taught shiny skin oss of function/weight bearing Tired/lethargic Disturbed sleep Loss of appetite Responds to antibiotics

Santy-Thomlinson 2011

Name	
Study Number	
Date of review/visit number	
Patient Group	
Checketts Otterburn score and pin identification letter	
Santy-Thomlinson classification and pin identification letter	
Patterson score (per pin)	
Swelling	
Redness	
Discomfort	
Loose	
Crusting	
Skin/ pin tent	
Drainage	
Reported problems with pins	
Reported problems with collars (if applicable)	
Use of antibiotics since last review	Oral/IV/None Type: Dose: Duration:
Hospital admissions since last review	
Additional consultations/ phone calls/ health care interactions	
Other infections since last review	Antibiotic use Yes/No
Self care or assistance required	
Work/exercise	

Demographics

Name	
Study Number	
Age	
Sex	
Occupation	
Injury/pathology	Open/closed
Time from injury to application of fixator	
Type of fixator	
Number of pins/ wires	Pins: Wires:
Current infection	Yes/No Type:
Co-morbidities	Osteomyelitis/ diabetes/ malignancy/ immunocompromised/ MRSA/ psoriasis/osteoporosis Other:
Current medication	Steroids/ DMARD/ ANT-TNF Other:
Other wounds	
Weight	Underweight/Average/Overweight/Obese
Draw pins/wires and identify using letters	

Appendix 12 –Evaluation of collars

Nottingham University Hospitals NHS Trust

The University of Nottingham

Name/identifier: Date completing form:

As part of the evaluation of the antimicrobial collar we would like to know about your experience using the device.

Please rate the following statements:

The collar is easy to apply

Strongly disagree Strongly agree

1 2 3 4 5

Any comments

The collar is comfortable to wear

Strongly disagree Strongly agree

1 2 3 4 5

Any comments

The collar does not irritate the skin

Strongly disagree Strongly agree

1 2 3 4 5

Any comments

The collar stays in place when applied

Strongly disagree Strongly agree

1 2 3 4 5

Any comments

The collar does not get in the way of my normal activities

Strongly disagree Strongly agree

1 2 3 4 5

Any comments

The collar is easy to clean and use

Strongly disagree Strongly agree

1 2 3 4 5

Any comments

Is there anything else you would like to tell the research team about your experience using the collar?

Thank you for taking the time to complete this questionaire. Your feedback is an important part of evaluating the product.

Appendix 13 – SPTT standard deviations

Mean and standard deviation data for SPTT

Day	F2903	SD	F3592	SD	F3451	SD	F2905	SD	F3412	SD	F3501	SD	F1693	SD
1	49.10	1.61	13.12	1.71	53.07	1.80	30.38	1.99	21.44	0.14	17.16	0.99	20.34	1.32
2	51.04	1.69	13.24	0.57	58.62	0.27	25.00	0.56	15.16	0.79	9.95	1.46	18.76	0.55
3	51.26	1.45	13.62	0.43	57.73	1.30	22.80	2.28	15.18	0.55	8.45	2.37	19.78	1.05
4	49.63	1.17	12.39	0.49	54.25	2.85	20.15	1.65	13.49	0.74	5.34	0.62	20.35	0.13
5	49.95	0.49	12.31	1.10	56.87	2.13	18.33	2.54	11.93	1.65	5.77	0.98	20.10	1.22
7	51.86	0.90	11.98	0.91	59.98	1.76	15.55	1.39	10.22	0.73	2.65	0.62	21.14	0.76
8	53.74	1.03	12.26	0.64	57.88	1.73	15.73	1.42	11.58	0.33	2.82	0.88	21.83	0.53
9	49.83	0.78	11.79	0.55	55.79	1.46	14.74	1.27	12.38	0.70	3.12	1.30	20.10	0.07
10	51.83	1.49	12.41	0.51	55.57	0.54	13.13	0.33	11.30	2.32	2.93	0.22	18.88	0.53
12	55.69	2.17	11.46	0.58	59.50	0.00	16.88	4.71	10.75	0.58	2.60	0.52	17.62	0.29
13	52.74	1.34	10.79	0.43	58.09	1.41	15.77	1.19	11.55	4.01	1.80	0.00	19.18	0.43
14	54.91	2.90	11.15	0.28	55.19	1.53	13.38	0.61	9.44	0.28	1.60	0.00	15.61	0.95
15	57.18	3.54	11.86	0.79	58.62	0.44	12.77	0.43	8.86	1.55	1.08	0.28	20.11	0.54
16	50.91	1.04	11.30	0.58	54.25	0.70	11.52	0.80	7.43	2.14	0.00	0.00	18.34	0.58
19	57.60	3.03	11.41	0.34	54.57	2.10	14.34	0.53	6.51	1.52	0.00	0.00	20.98	0.47
20	54.51	1.42	11.19	1.43	54.12	2.30	13.60	0.17	4.86	1.31	0.00	0.00	19.57	0.66
21	51.76	1.32	11.57	1.76	56.28	0.97	14.10	0.39	5.29	2.31	0.00	0.00	20.09	0.22
22	53.76	3.88	11.21	0.52	57.87	3.38	13.73	0.77	5.08	1.21	0.00	0.00	15.63	1.31
23	56.44	1.73	10.26	0.30	55.27	1.11	10.81	0.51	2.83	1.10	0.00	0.00	18.07	0.41
29	57.52	0.62	8.31	1.28	51.46	0.95	9.55	0.09	2.26	0.71	0.00	0.00	15.18	0.50
34	53.00	1.91	10.87	0.70	52.37	0.12	9.20	0.30	0.17	0.29	0.00	0.00	16.60	0.10
35	54.76	2.91	9.70	0.35	50.17	0.95	9.60	0.30	0.00	0.21	0.00	0.00	16.27	0.52
36	54.22	3.14	9.07	0.23	48.60	0.50	9.03	0.49	0.17	0.23	0.00	0.00	15.60	0.26
37	46.78	1.86	9.40	0.20	47.60	0.69	8.53	0.65	0.63	0.23	0.00	0.00	15.51	0.06
41	50.79	4.97	10.75	0.75	46.49	0.26	10.35	0.76	5.19	3.84	0.00	0.00	17.45	0.95
42	47.32	1.83	9.72	0.51	45.56	0.82	10.72	0.27	3.06	2.52	0.00	0.00	16.76	0.34
43	50.25	0.26	9.06	0.87	48.05	2.33	11.53	0.98	3.10	14.49	0.00	0.00	17.19	0.55
48	49.39	1.12	8.12	0.36	45.13	1.20	9.19	0.30	0.00	0.00	0.00	0.00	16.54	0.76
49	53.86	0.42	9.45	0.14	48.74	0.32	10.01	0.39	0.00	0.00	0.00	0.00	13.94	0.49
50	55.06	1.01	8.30	0.75	46.30	0.26	7.73	0.72	0.00	0.00	0.00	0.00	13.45	0.54
55	47.48	0.34	8.17	1.01	43.72	2.70	8.61	1.05	0.00	0.00	0.00	0.00	14.74	0.58
56	51.22	1.35	9.71	1.11	44.65	1.41	8.00	0.79	0.00	0.00	0.00	0.00	13.49	0.69
57	50.68	2.20	8.73	0.26	44.30	1.53	8.47	0.40	0.00	0.00	0.00	0.00	12.82	0.57
62	51.22	1.10	8.51	0.29	39.30	3.19	5.81	0.13	0.00	0.00	0.00	0.00	12.96	1.08
69	44.63	1.28	7.32	1.16	45.13	0.77	8.93	0.40	0.00	0.00	0.00	0.00	15.99	2.28
70	51.11	1.38	9.19	0.91	42.03	0.76	4.83	1.20	0.00	0.00	0.00	0.00	14.98	2.21
71	48.51	1.93	7.54	0.41	42.88	1.34	6.91	0.70	0.00	0.00	0.00	0.00	14.77	1.73
76	48.01	2.81	7.97	0.91	44.52	2.44	11.47	0.46	0.00	0.00	0.00	0.00	16.92	1.75
77	46.20	1.15	8.07	1.37	44.75	0.86	4.92	0.30	0.00	0.00	0.00	0.00	14.08	1.44
78	43.02	0.32	7.62	0.54	42.51	0.82	4.39	0.31	0.00	0.00	0.00	0.00	14.18	1.85
83	46.47	2.00	7.34	0.34	44.01	1.07	4.65	0.32	0.00	0.00	0.00	0.00	14.52	2.33
84	43.66	3.30	7.67	0.89	43.48	1.04	5.46	0.55	0.00	0.00	0.00	0.00	15.50	1.44
85	47.66	1.40	7.95	0.75	43.00	0.80	5.71	0.62	0.00	0.00	0.00	0.00	14.09	1.77
90	46.75	1.88	7.40	1.08	44.32	1.26	4.31	0.57	0.00	0.00	0.00	0.00	15.04	1.16
91	45.47	2.47	8.30	1.04	46.27	0.59	4.49	0.16	0.00	0.00	0.00	0.00	14.40	1.84
97	44.84	0.33	7.10	0.44	40.64	2.64	4.73	0.53	0.00	0.00	0.00	0.00	2.93	2.38
99	45.66	0.77	0.00	0.00	40.08	1.14	4.73	0.33	0.00	0.00	0.00	0.00	14.20	1.39
104	44.04	1.26	0.00	0.00	42.88	0.69	3.75	0.68	0.00	0.00	0.00	0.00	13.12	0.89
107	43.52	1.18	0.00	0.00	39.83	1.02	4.06	0.62	0.00	0.00	0.00	0.00	13.99	1.30

Median ZoI and Standard Deviation for SPTT with clindamycin and rifampicin using F2903

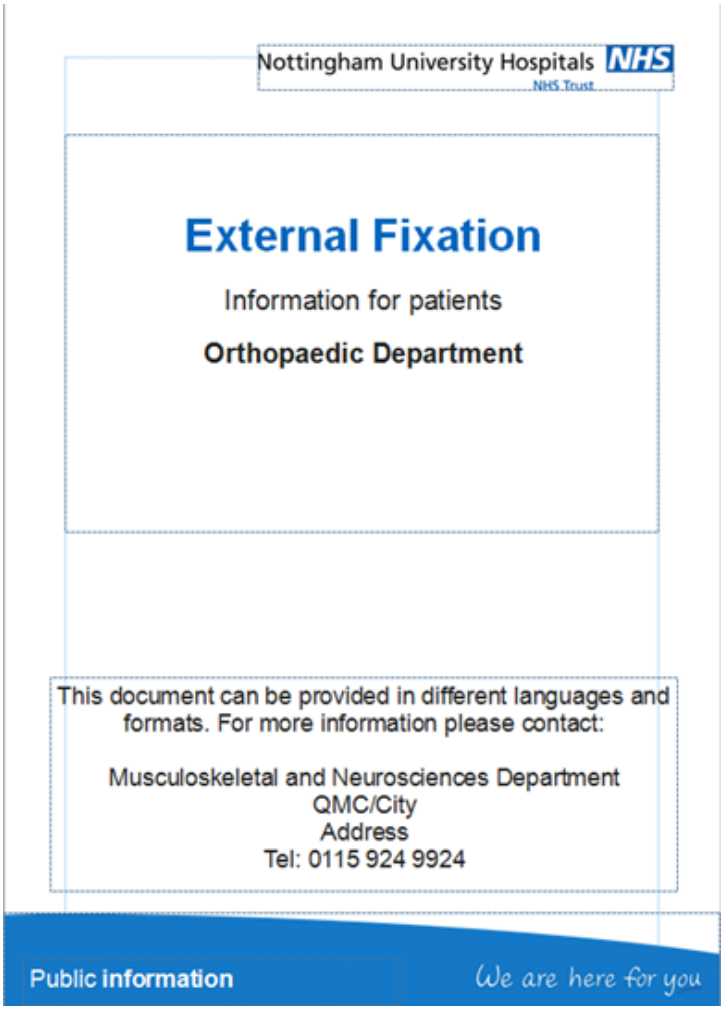
Day	C 0.2%	SD	C 0.1%	SD	R 0.2%	SD	R 0.1%	SD
1	7.22	2.62	10.21	4.17	24.95	1.26	24.57	0.32
2	3.14	0.46	4.17	1.58	17.53	1.80	17.29	0.84
3	2.39	1.17	3.59	1.31	17.99	2.30	11.85	0.38
4	0.50	0.86	2.24	1.25	13.50	1.42	10.93	1.08
8	0	0.00	1.73	0.73	8.21	1.38	5.16	1.07
10	0	0.00	1.31	1.25	5.53	1.82	4.13	1.16
11	0	0.00	0.00	0.00	6.11	0.34	3.20	0.85
14	0	0.00	0.00	0.00	2.68	0.82	0.55	0.48
15	0	0.00	0.00	0.00	0.46	0.79	0.46	0.79
16	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00

C = Clindamycin R = Rifampicin SD = Standard Deviation

Median ZoI and Standard deviation for Triclosan SPTT using F2903 and F1693

Day	T 1% F2903	SD	T0.5% F2903	SD	T 1% F1693	SD	T0.5% F1693	SD
1	47.99	2.80	46.89	1.48	19.70	0.23	20.42	0.91
2	46.83	0.17	46.40	0.48	18.36	0.71	19.79	0.58
3	41.50	0.40	44.19	1.14	19.65	0.64	20.13	0.66
4	41.21	2.66	44.61	0.69	18.99	1.06	20.20	0.21
8	45.91	1.65	46.34	1.15	16.14	0.33	16.28	0.93
10	42.38	0.28	44.31	0.82	19.10	2.86	17.67	0.60
11	43.13	0.46	46.00	0.87	17.46	0.81	17.55	0.49
14	41.51	1.53	42.51	0.43	16.19	0.50	17.42	0.56
15	41.95	1.01	44.21	0.45	17.87	1.85	18.38	0.83
16	43.84	0.71	45.58	1.52	16.93	0.62	17.76	1.93
17	48.10	10.06	43.07	0.08	17.37	0.68	17.49	0.50
18	43.90	0.59	44.69	1.97	16.40	0.63	16.97	0.79
21	43.68	2.26	46.38	1.68	18.86	1.08	18.94	0.45
22	44.93	0.46	46.07	0.55	18.57	0.69	18.70	0.87
23	46.28	1.96	47.43	1.17	17.29	0.58	16.82	0.34
24	41.49	0.90	42.44	0.47	19.20	1.33	18.50	0.13
25	39.26	0.87	39.33	0.88	17.08	1.00	17.45	0.45
28	41.26	0.54	40.80	0.69	15.52	0.39	16.39	0.48
30	42.87	1.62	43.20	0.56	16.55	0.64	17.81	0.62
31	46.25	7.88	55.93	1.72	15.29	0.20	16.40	0.61
32	49.41	1.19	52.59	0.69	16.80	0.58	15.04	0.45
35	52.52	0.91	53.69	0.76	16.01	0.75	16.29	0.09
37	45.03	1.27	43.94	0.66	16.22	0.72	15.30	0.73
39	44.60	2.67	44.80	1.05	15.00	0.35	17.63	2.66
42	47.96	1.04	47.78	0.34	17.12	0.47	17.76	0.31
43	43.65	0.37	42.79	1.39	17.26	0.58	17.25	0.27
44	43.17	0.26	42.18	0.70	16.15	0.64	14.81	0.48
45	45.71	0.22	46.07	0.46	16.49	1.17	17.27	0.23
46	45.10	1.27	44.64	1.57	15.69	0.70	16.86	0.21
47	40.65	0.21	39.86	0.47	14.30	0.75	14.66	0.24
48	40.49	1.58	40.37	0.91	16.27	0.70	16.45	0.61
49	39.43	0.37	40.58	0.88	15.25	0.20	15.03	0.58
52	41.20	0.17	40.63	0.91	14.00	0.35	14.33	0.23
55	43.38	0.47	43.39	0.14	15.51	0.51	15.37	1.43
56	38.43	0.68	40.53	0.62	13.01	0.31	14.06	0.69
59	39.23	0.70	40.96	0.88	14.60	0.34	15.75	0.53
60	38.21	1.43	40.88	0.29	13.28	0.18	15.57	0.35
61	38.15	0.83	36.19	0.75	14.12	0.26	15.68	0.55
62	39.88	0.96	42.01	0.33	12.80	0.59	14.81	0.21
63	38.44	1.13	42.55	0.75	12.76	0.61	14.23	0.98
67	38.28	1.03	41.26	0.78	13.54	0.28	14.22	0.47
69	45.21	0.22	41.03	1.35	12.84	0.64	15.32	0.06
73	42.13	0.93	45.31	0.57	14.80	0.62	12.69	0.36
74	42.35	0.48	41.25	0.76	11.50	0.72	13.19	3.57
77	40.54	0.86	37.92	0.37	12.51	0.23	13.18	0.27
80	42.61	0.84	44.40	1.28	12.59	0.26	13.98	0.24
82	42.69	1.15	39.95	0.73	12.54	0.95	13.29	0.45
86	38.25	0.60	39.48	1.43	10.81	0.49	11.80	0.43
91	33.65	1.64	38.20	2.07	9.58	0.69	12.09	0.38
94	40.86	1.58	44.03	1.00	10.17	0.03	11.44	0.38
98	38.90	1.89	39.29	1.30	9.57	0.07	11.39	0.44
100	37.19	1.00	38.75	0.82	10.94	0.65	12.55	0.03

Appendix 14 – External fixator patient information leaflet



Nottingham University Hospitals NHS
NHS Trust

External Fixation

Information for patients

Orthopaedic Department

This document can be provided in different languages and formats. For more information please contact:

Musculoskeletal and Neurosciences Department
QMC/City
Address
Tel: 0115 924 9924

Public information

We are here for you

Clothing

You will be able to wear normal clothes while you have the frame on, although you may need clothes which are looser than you would usually choose, so that they can fit over the frame. For example loose fitting jogging bottoms. In warmer months loose fitting shorts or skirts are easy to wear. Many people have found a local seamstress to make modifications to clothes for special occasions, or to make special items such as trousers with built in foot cover (like a 'onsie') to help keep the foot and leg warm in winter.
Here are a few other ideas:

- Velcro fastenings added to the side of shorts or trousers to make them easier to get on/off
- Extra panels of material added to trousers to allow them to fit around the frame
- Using bikini bottoms that tie at the side as underwear. They are easy to get on over the frame (without having to buy larger underwear), and easy to remove for bathroom purposes.
- Make a 'leg warmer' for your frame. This could be done in several ways such as material fastened with Velcro or popper studs, or a material tube with loose elastic attached at the top and bottom. It will help to keep your leg warm, and can stop the frame snagging your clothes.

Some simple tips

Do:

- Use a separate piece of gauze to clean each pin site (you may spread infection otherwise)
- Call the hospital if you think you have an infection or you have any worries

Do not:

- Do not allow animals to lick the pin sites or frame area
- Do not go swimming in the ocean or lakes
- Do not sit in a bath and soak your frame in the water
- Don't suffer pain for the sake of it. Take pain killers if you need them.

fracture to heal or up to one year for more complicated procedures. Each frame is individually designed depending on the person and the condition being treated. It is important that you try to keep active while you have your frame on, as this will help the bone to heal and help you get back to your normal activities sooner. You will have 'good' days and 'bad' days. If you feel that you are struggling please let the nurse specialist or consultant know.

Sometimes changes will need to be made to the frame so that the bones can heal in the best position. This procedure will be explained to you by the nurse specialist. The nurse will help you the first time you need to do this. When you are making adjustments to your frame, you may feel more discomfort due to the change of position. You can take regular pain killers to help with this pain. If you have any problems or concerns, please contact the nurse specialist.

When the bone is healed the frame will be loosened (dynamised) to see if you are able to put weight though you leg. This is to test the strength of the new bone. If there are no problems, the frame can be removed. Depending on how you feel the frame can be removed in clinic, or you can come in to hospital and have an operation to take the frame off. After the frame is taken off you may need to have a cast or boot applied for a few weeks while the bone finishes healing.

Once the frame is removed you may have some small scars from where the pins and wires were. These will fade gradually over time.

Caring for your pin sites and your frame

It is very important that the frame and pin sites are kept clean to prevent infection. If the pin site becomes infected you may need antibiotics to treat the infection or the pin may need to be removed. In serious cases infection can get in to the bone (osteomyelitis). This can delay bone healing, and you may need to be admitted to hospital for antibiotics and an operation. In severe cases the frame may need to be removed completely.

The aim of pin site care is to reduce the risk of infection. Please check your pin sites everyday for signs of infection. If you experience any of the following signs of infection please contact the nurse specialist or any of the numbers in this leaflet as you may have an infection.

Signs of infection

- Skin redness
- Warmer at the pin or wire site
- Pain
- Swelling
- Increased discharge or oozing at the pin or wire site.
- Changes in the colour, consistency or smell of the drainage
- Fever, or high temperature of 38°C or over
- Movement or looseness of the pin or wire.

If you are suffering with dry skin you can apply body lotion to the skin, although avoid the areas when the pins/wires go in to your skin.

Some of the pins may have sharp edges which may catch on your clothes or bed sheets. Applying tape to the end of the pins can help reduce how much they catch.

How to care for your pin sites

The aim of pin site care is to:

- Minimise the risk of infection
- Promote healing
- Prevent problems with the surrounding skin

Your nurse will discuss with you how often your pin sites need to be cleaned. This can vary depending upon the type of external fixator and the position it is in. Your nurse will show you how to care for your pin sites before you are discharged from hospital and this sheet is to help remind you of the correct procedure.

You will need:

- A stable surface to put your dressings onto that can be wiped clean with hot, soapy water or a disinfectant wipe before and after use
- Liquid soap
- Access to hot water for hand washing - the correct hand washing technique will be shown to you by your nurse
- Clean towel which will need to be kept for pin site care only. This must be washed after each time you clean and dress your pin sites. Alternatively you can use disposable kitchen paper roll.
- Hand rub solution (if you are doing your own care)
- Sterile sponges or gauze
- Sterile gauze swabs
- Sterile scissors if dressings require cutting. Single use disposable scissors need to be thrown away after each use.
- Dressings (if required) will be provided by healthcare professionals
- Chlorhexidine as a cleaning solution
- Sterile gallipot
- Waste bag

Step 1: Preparation- Getting the equipment ready

1. Clean and dry the surface you are going to put your dressings onto. This can be done using hot, soapy water and a clean cloth. Wipe all over the surface you are going to use, then dry it with a clean cloth or kitchen paper towel. Alternatively you may choose to use a disinfectant wipe.
2. Wash your hands using liquid soap and water and dry well with a clean towel.
3. Open all the necessary cleaning equipment and dressings you will need and put onto your clean surface. Pour cleaning liquid into the gallipot.
4. Have your waste bag close by and open ready for use.
5. Avoid touching any open wound area with bare hands.

Step 2: Removing your dressing and checking the pin sites

1. Remove the dressings and place these into the waste bag.
2. Look at each pin site for any signs of infection, which are redness, swelling, smell and thick yellow discharge or pus. If any of these signs are present, clean these pin sites last and use the contact information at the end of this leaflet if you are worried about your pin sites.

Step 3: Cleaning the pin sites

1. Use the hand gel and repeat the hand washing technique.
2. Using the sponges or gauze, clean each individual pin with an outward rolling motion away from the pin.
3. Use one sponge/gauze for each wipe and discard. Do not dip your sponge/gauze back into the cleaning fluid once it has been on the skin, use a fresh wipe. Always finish one pin site before moving on to the next one. Keep using clean wipes until all pin sites are clean.
4. Check that your skin is not stuck to the pin and that it moves easily and freely around each pin site as you are cleaning.

Step 4 : Applying dressings (if necessary)

1. Use the hand gel and repeat the hand washing technique.
2. Apply the dressings the nursing staff have advised and shown you how to use. These will vary depending upon the condition of your pin sites.
3. Dispose of all the equipment you have used into the waste bag.
4. Wash your hands with liquid soap and water.
5. Clean and dry the surface you have used for your dressings.
6. Hand towel to be washed after each use.
7. Keep all equipment in a clean, dry place.

Terminology - jargon-buster

Here are some of the common terms you may hear during your admission

Ilizarov fixator – this is a type of external fixation device

Taylor spatial frame – this is a type of external fixation device

Half pins – screws that are placed in to your bone and attached to the frame to stop your fracture from moving

Wires – wires are inserted though the soft tissue and bone and attached to the frame

Fracture – a break in the bone

Osteomyelitis – infection of the bone

Struts – a part of the frame which can be used for changing positions of the frame

Distraction – the process in which the cut ends of the bone are separated and gradually pulled apart

Compression – the process in which the cut ends of the bone are pushed together

Feedback

We appreciate and encourage feedback. If you need advice or are concerned about any aspect of care or treatment please speak to a member of staff or contact the Patient Advice and Liaison Service (PALS):

Freephone: 0800 183 0204
From a mobile or abroad: 0115 924 9924 ext 65412 or 62301
E-mail: pals@nuh.nhs.uk
Letter: NUH NHS Trust, c/o PALS, Freepost NEA 14614, Nottingham NG7 1BR

www.nuh.nhs.uk

If you require a full list of references for this leaflet please email patientinformation@nuh.nhs.uk or phone 0115 924 9924 ext. 67184.

The Trust endeavours to ensure that the information given here is accurate and impartial.