Investigating the effectiveness of dialkylcarbamoylchloride-coated wound dressings in the prevention of surgical site infection

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ABSTRACT

Background: Surgical site infection (SSI) is the second most common healthcare acquired infection and may complicate between 5 and 30% of all surgical procedures. Avoidance of antibiotic or antimicrobial agents is important to future prevention strategies due to increasing levels of microbial resistance. When impregnated into post-operative dressings, dialkylcarbamoylchloride (DACC) non-selectively binds bacteria at the wound surface which may prevent ingress into the wound thus reducing SSI rates.

Methods: Following a systematic review of the evidence, two studies were undertaken; the first a non-randomised before-and-after study in which 100 consecutive patients received a control dressing and the following 100 patients received a DACC-coated dressing; and the second a pilot feasibility randomised controlled trial in which 144 patients were recruited and randomised to receive either a DACC-coated dressing or a control dressing.

Results: In the first study, the rate of SSI at 5-7 days was significantly lower in the DACC group compared to standard dressings (1% Vs 10%, $p < 0.05$). There was no difference in the rates of SSI at 30 days (10% vs 19%, $p = 0.11$). In the second study, at 30 days, there was a 36.9% Relative risk reduction in SSI associated with the DACC-coated dressing (16.22% vs 25.71%, odds ratio 0.559, p = 0.161). In patients who had a prosthetic implant, there was a reduction of SSI from 24% to 7.7% at 30 days (OR 0.264, p = 0.109). In terms of feasibility, 43.5% of screened patients were successfully randomised in the study, with a retention rate of 76.4% across the trial.

Conclusions: The work in this thesis has shown that DACC-coated dressings show a promising effect in the reduction of SSI, and that a large randomised study is both feasible and justifiable. This pilot data justifies the completion of a wider multicentre study to further assess the clinical and cost effectiveness of this dressing technology.

PRESENTATIONS

Totty JP, Cai P, Hitchman L, Harwood A, Wallace T, Carradice D, Smith G, Chetter I. "Dialkylcarbomoylchloride (DACC) coated dressings may reduce the rate of surgical site infection when used to cover incisional wounds post-operatively." *In* the European Wound Management (EWMA) Conference 2019, Gothenburg, Sweden, 7th June 2019.

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AUTHOR'S DECLARATION

I confirm that this work is original, and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information used to produce this piece of work has been appropriately anonymised.

CHAPTER 1: INTRODUCTION

Figure 1 - Image of Achilles bandaging the arm of Patroklos, from an ancient Greek vase c500 BC[6]

1.1 A Brief History of Wound Care

Since the Neolithic era, man has been attending to his wounds. Wound care evolved from magical incantations, potions, and ointments, to a systematic text of wound care and surgery from Hippocrates and others. At the fall of the Roman Empire, advances in wound care were lost, and in Europe, in the Middle Ages wound care regressed back to that of potions and charms. There were no significant advances in wound care until the 19th and 20th Centuries, in which warfare and the industrial revolution brought it to the fore once more.[7] Since that point, advances in wound care have been frequent and significant, bringing us to the modern age.

1.1.1 Ancient Origins of Wound Management

The Sumerians are believed to have produced the first written evidence of man's attention to wounds and wound healing. These were in the form of stone tablets believed to be older than 2,000 BC. Such tablets describe treatment of injuries in the

form of either spiritual incantation or by washing of the wound with beer followed by the application of a *poultice*, or paste. Ingredients of these poultices mentioned in the tablets include dust, plants, mud, milk, wine, beer, oil and flour.[7-9]

1.1.2 The Ancient Egyptians

The Ancient Egyptians appear to have undertaken more advanced wound management practices still than their Sumerian predecessors. They had a myriad of therapies, believing wounds to be an entry point for evil spirits to the body.

The Edwin Smith Surgical Papyrus, dated 1,650 BC, describes 48 cases of wounds, and includes instruction on examination, determining severity and subsequent treatment. In addition, contained within the Edwin Smith Papyrus is the description of an "inflamed," "reddened," "hot" wound, suggesting that the Egyptians were able to recognise the signs of inflammation and infection,[10, 11] and demonstrating that the Egyptians were able to distinguish between infected and non-infected wounds and manage them accordingly.[12] The Egyptians also offered treatment based on both diagnosis and prognosis, showing an increasing sophistication of medical practitioners.[13]

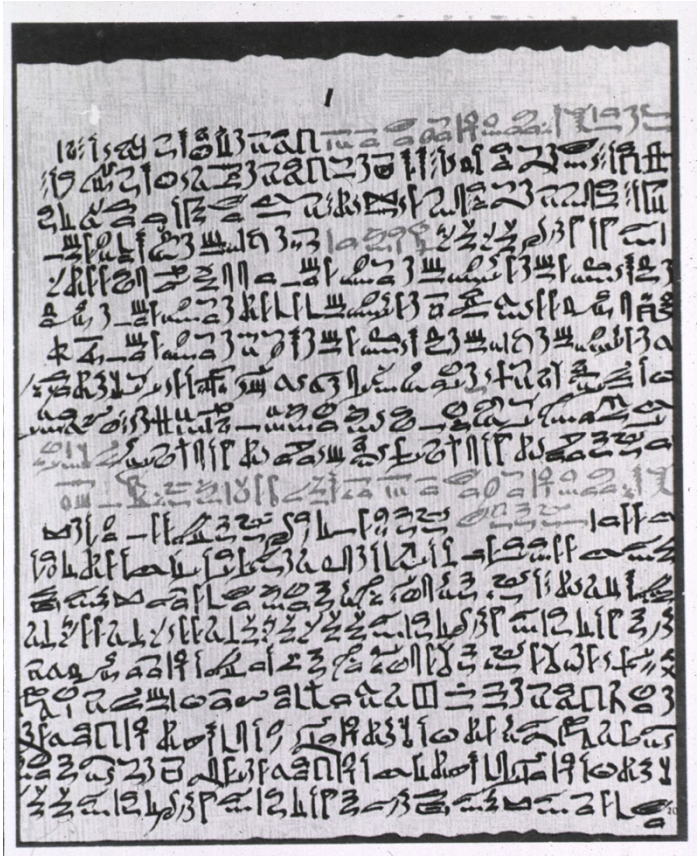


Figure 2 - The Ebers Papyrus, c1500 BC.[3]

Approximately 100 years later, the Ebers Papyrus, circa 1,500 BC, outlined a number of therapies for the treatment of wounds. Almost half of the therapies consisted of products from animals, including cows, geese, donkeys, hippopotamuses, pelicans, snake, tortoise and crocodiles. Remarkably, over 50 of these prescriptions are believed to contain faeces as an active component, for internal and external application.[10, 14]

Honey was by far the most popular Egyptian 'drug,' unsurprising given that the antibacterial effects of honey, particularly as a topical agent, are well documented.[15] Other therapies included wine, frankincense, turpentine, acacia gum, lint and animal grease.[10, 16] The Egyptians displayed their prowess in applying bandaging when embalming the dead, but the same skills were utilised on the living. Bandages were used to cover and keep in place the medications described above. Additionally, the Egyptians were the first to describe what we now refer to as stitching of wounds in order to bring skin edges of clean cuts together.[10]

1.1.3 The Ancient Greeks

Much like the ancient Egyptians, the Greeks were forward thinking in their medical management. They too were able to distinguish between infected and non-infected wounds, and documented their experiences of wounds in their writings.[17] Hippocrates (460-377 BC) used vinegar to irrigate open wounds, and wrapped dressings, termed a *Sphedóne*[7] around wounds to prevent further injury. He washed ulcers with wine and dressed them with fig leaves.[17-19] Later, Galen of Pergamum (120-201 AD) who was a notable "game doctor" – Doctor to Gladiators – experimented with various coverings on the wounds of combatants. He recognised that wounds healed best in a continuously moist environment and describes providing this moist environment with what was likely a cotton cloth and a sponge, referring to the difficulty of keeping dressing moist in the summer.[8] He also noted that pus from wounds precluded healing.[18, 20]

1.1.4 The Middle Ages and Renaissance

Following the fall in the Roman Empire around 300-400 AD, Europe entered a period of intellectual stagnation known as the Dark Ages. The study of medicine was deemed inferior to the study of theology, stunting its advances throughout this period. Theologians divided medicine into two parts: religious medicine, concerned with "heavenly things"; and human medicine, concerned with "earthly things"; Human medicine relied on empirical methods such as dietary management, drugs, bleeding, and simple surgical operations. Religious medicine involved prayers, penitence, exorcism, holy relics, charms, and incantations.[21, 22]

Medieval surgeons (at this point in history very separate from physicians) continued to use potions made of wine, egg, honey and beer to cleanse and dress wounds much like their earlier counterparts.[23-25] Individuals, however, did continue to innovate. Theodoric, Bishop of Cervia (1210-1298), may have been the most ingenious of medieval surgeons. He rejected the idea that the formation of pus was a natural and necessary stage in the healing of wounds, realising that the generation of pus (sometimes deliberately provoked by surgeons), actually obstructed wound healing. He also objected to the use of complex and noxious wound dressings.[21] In general,

however, wound care, and medicine as a discipline, was subject to a decline in innovation[26].

The Renaissance denotes the rebirth of the study of the arts and sciences in Europe, between the 14th and 17th Century.[11, 27] During this period, the study of the human body and its anatomy flourished, as did the modern scientific method. Wound care, however, remained limited to the application of bandages or poultices, and the materials used changed very little in this time.[8]

1.1.5 The 19th and 20th Centuries

Unlike other areas of medicine, wound care is relatively modern in its advances. Only by the 19th and 20th Centuries did we see significant advances in wound dressings and wound therapies. This was aided by the discovery of antiseptics, and the role they play in reducing mortality from surgical or traumatic wounds.[8] Phillip Semmelweis (1818-1865) is regarded as a pioneer of antisepsis, after observing that women in his obstetric clinic were more likely to suffer from puerperal fever (with an associated mortality of 35%) if they were treated by medical students who had attended clinic directly from the anatomy laboratory, where they practiced cadaveric dissection. These findings encouraged him to instigate a policy of hand washing with chlorinated lime between procedures. The findings of his study resulted in a reduction of mortality of around 90%.[28]

Following on from the work of Semmelweis, an English surgeon named Joseph Lister (1827-1912) further realised that antiseptic substances would not only be beneficial for hand-washing, they could also be used to treat the instruments used during procedures, and that the surgical environment could reduce infection rates. Lister chose to soak his instruments and bandages in carbolic acid, and then sprayed the operating area with the same substance prior to performing surgery. These actions prompted a fall in mortality from 50% to 15%.[8] Iodine, first described in 1839, was used during the American Civil War (1863) and World War I to treat wounds and scrub hands before surgery.[29] Robert Wood Johnson, after hearing Lister speak of his methods, set out to develop antiseptic dressings, founding *Johnson and Johnson* in

the process. He developed surgical dressings by sterilising cotton and gauze with dry heat followed by steam and pressure.[7]

These findings revolutionised the surgical environment and the surgical management of wounds. This was reflected in wound care textbooks from the 1880's which outline the importance of skin cleansing and wound irrigation with carbolic acid, a direct result of Lister's and Semmelweis' findings.[7]

Whilst hand washing to reduce infection rates was becoming increasingly common practice, the routine use of gloves, gowns and masks was unheard of until the late 19th Century. The pioneer of "personal protective equipment" was Dr William Halsted (1852–1922). Dr Halstead introduced the use of rubber gloves to his scrub nurse because she was developing skin irritation from the chemicals used to disinfect instruments. The routine use of surgical gloves was introduced by Halsted's student Joseph Bloodgood. Halstead also advocated the use of silver foil dressings for wounds.[7, 30]

The development of modern warfare brought to the operating table wounds inflicted by guns and bullets, and contaminated with shrapnel and material from the trenches.[9, 11] One of the last pioneers of modern surgical wound management was the Belgian army surgeon Antoine Depage (1862-1925). Depage, who was active during World War I, is credited with the advent of modern wound debridement. Depage, during exploration of the wound, cleared the wound of debris and foreign material. He also removed damaged or necrotic tissue, realising that this provided an ideal environment for the growth of pathogens.[7]

In 1829, Napoleon's surgeon-in-chief, Baron Larrey, reported that when maggots were found in battle injuries, they prevented the development of infection and accelerated healing.[31] Zacharias, a confederate medical officer (surgeon) during the American civil war (1861–1865) was the first Western physician to intentionally introduce maggots into wounds.[32]

By the 1950s, the textile industry was producing a myriad of synthetic fibres that clinicians were incorporating into wound coverings, and beginning to combine these

practices with new knowledge of antimicrobials.[33] George Winter,[34] like his earlier Ancient Greek colleagues identified that a moist wound environment greatly improved the rate of wound healing, after covering wounds with a polythene film. It was his discovery that formed the basis for modern, occlusive dressings that promote a moist wound environment, as well as introducing a focus on evidence-based best practice.

1.2 Wounds and Wound Healing

1.2.1 Anatomy of the Skin

The skin, or *integument* (derived from the Latin *integere,* to cover), is regarded as the largest organ in the human body. It consists of an outer layer, the epidermis, and a deep layer, the dermis. Deep to the dermis is the subcuticular layer of tissue. Each layer can be further subdivided based upon their structure, function and histology.[35] The anatomy of the skin contributes to the functions of the skin as a protective organ.

1.2.1.1 Epidermis

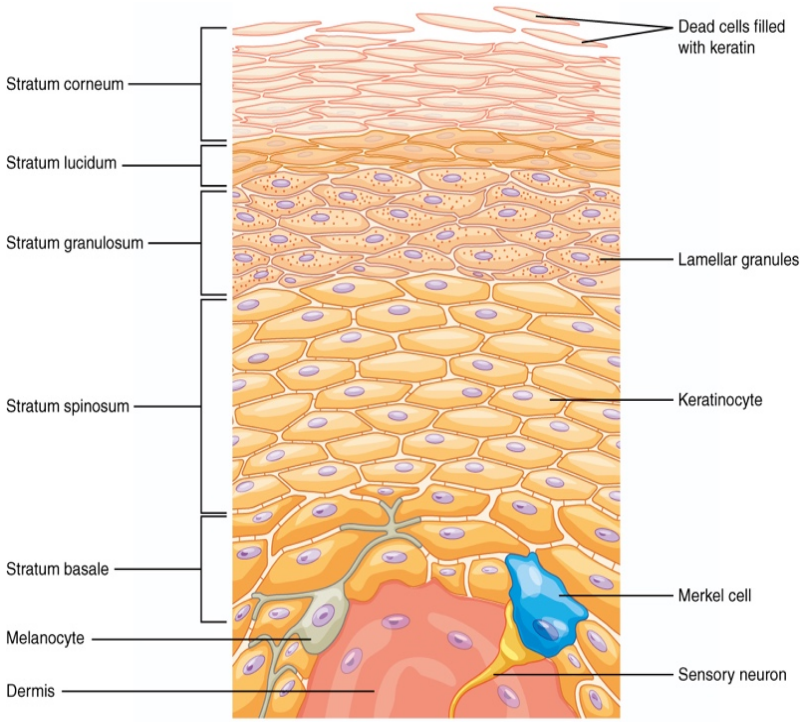


Figure 3 - Layers of the epidermis[5]

The epidermis is a stratified squamous epithelium consisting of keratinocytes, the most abundant cell type, that are keratinised cells that change in characteristics as

they mature; melanocytes, pigment producing cells that protect from ultraviolet (UV) radiation; Langerhans' cells, an antigen-presenting cell responsible for recognising new allergens and initiating an immune response; and Merkel cells, that are, as yet, poorly understood, but thought to be responsible for light touch sensation.[36] The epidermis may be divided into four layers[5, 37]:

Stratum Basale (Basal cell layer)

This is generally one cell thick, consisting predominantly of dividing or non-dividing keratinocytes.[35, 37]

Stratum Spinosum (Spinous layer)

Basal cell keratinocytes migrate towards the surface and form a layer of polyhedral cells joined by desmosomes (a strongly binding junction between two cells[38]).[35, 37]

Stratum Granulosum (Granular cell layer)

Cells within the granular layer contain granules of lipid that, when discharged, maintain the barrier function of the skin.[35, 37]

Stratum Corneum (Horny layer)

This is the outermost layer of the skin. Keratinocytes within the stratum corneum (corneocytes) have lost their organelles, including the nuclei. They are flattened and arranged into macrofibres. The thickness of this layer is variable according to the area of the body it covers. It provides a protective layer against mechanical insults and pressure.[35, 37]

1.2.1.2 Dermis

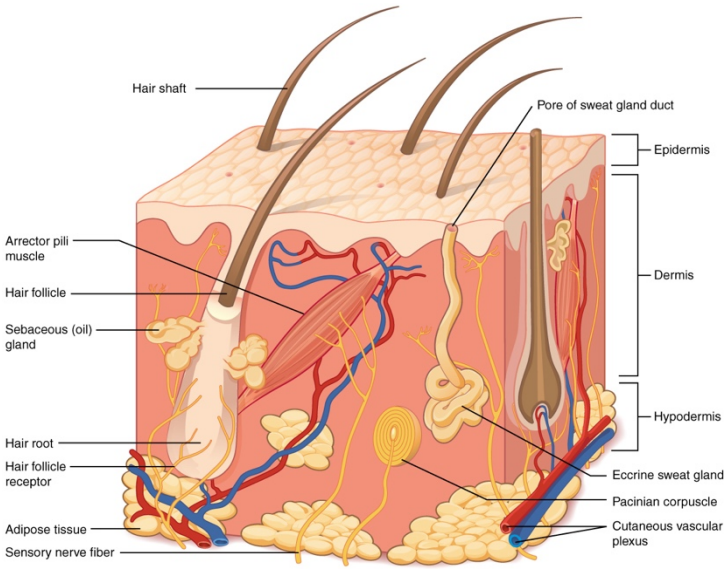


Figure 4 - Structure of the skin[4]

The dermis lies deep to the stratum basale of the epidermis, and can itself be divided into the papillary dermis and the reticular dermis. It provides protection against mechanical forces, and contains several specialised structures.[39]

The papillary dermis is the thinner, superficial layer of the dermis, which interdigitates with the rete ridges of the epidermis.[35, 39] Within this layer are fibroblasts, adipocytes, phagocytes, Meissner corpuscles (touch receptors) and multiple capillaries.[5]

The reticular dermis is the thicker of the two layers, and is composed of dense connective tissue. It is well vascularised and has a good nervous supply (sensory and sympathetic). The term *reticular* is derived from the Latin *rēticulum*, net-like, and is used to describe the appearance of the fibres within this layer. Elastin fibres provide elasticity to the skin, whilst collagen fibres provide structure and tensile strength.[35]

1.2.1.3 Hypodermis

The hypodermis, or subcuticular/subcutaneous layer, is the layer of fat deep to the dermis, containing nerves, blood vessels and lymphatic tissues.[36, 37, 39]

1.2.1.4 Structures within the skin

Blood Vessels

The blood vessels of the skin are arranged in two layers – a deep and superficial plexus. The deep plexus lies just superior to the subcutaneous fat, and supplies the sweat glands and hair follicles with oxygenated blood. The superficial plexus is in the papillary dermis, and its arterioles form capillary loops in the papillae. This rich network of anastomoses play an important role in thermoregulation.[40]

Nerves

The majority of free-end sensory nerves are found in the dermis of the skin, detecting pain and heat stimuli. Specialised nervous organs, Pacinian and Meissner corpuscles, act as pressure receptors, sensing deformity of the skin, vibration and touch.[40]

Hair

The dermis contains hair and hair follicles, consisting of a hair bulb, papillae, sebaceous and sweat glands and an erector pili muscle. Hair plays a role in thermoregulation and cosmesis.[35]

1.2.2 Definitions

A wound is defined as damage or disruption to the anatomical structure of the skin, which may be limited to the epithelium or extend deeper in the dermis or subcutaneous tissues, involving structures such as blood vessels, nerves, musculature, tendons, organs or bone. They may arise as a result of a pathological process, or be inflicted in an accidental or intentional insult.[41] Wound healing is the complex biological process that restores skin integrity following such an insult.[42]

1.2.3 Acute and Chronic Wounds

Time is a crucial factor in wound healing, and wounds can therefore be clinically divided into 'acute' and 'chronic' based upon the time taken to heal. Acute wounds are wounds that progress through the stages of healing in a normal and timely fashion, normally between 5 and 10 days, and certainly within 30 days. The end result of such a process is a restoration of both anatomy and function.[41]

Chronic wounds are wounds that do not proceed in the same fashion, often as a result of prolonged inflammation, leading to incomplete healing, although the length of time needed for a wound to be defined as chronic is disputed.[41-43] There are

multiple factors that may impair the healing process and lead to the development of a chronic wound.

1.2.4 Stages of Wound Healing

Wound healing is a complex process involving multiple pathways, that can be divided into four principle phases:

1.2.4.1 Haemostasis

Immediately following an injury or incision, the first action of the body is to prevent exsanguination. Damaged vessels constrict through the action of smooth muscle in the vessel wall. Vessels up to 5mm in diameter may close completely through this action (assuming the injury is in the transverse plane). However, tissue hypoxia as a result of this vasoconstriction causes an acidosis, promoting the production of nitric oxide and other metabolites that cause a passive and reflexive vasodilatation, causing the resumption of bleeding.[41, 42, 44].

Simultaneously, histamine release from mast cells acts to increase vascular permeability, allowing the influx of inflammatory cells into the extra-cellular space. This histamine effect causes the characteristic hot, red, swollen appearance of a fresh wound.[42]

Together with these events, further blood loss is prevented by platelet aggregation and the formation of a clot, through the activation of the intrinsic and extrinsic coagulation cascades (figure 5).[41, 45, 46]

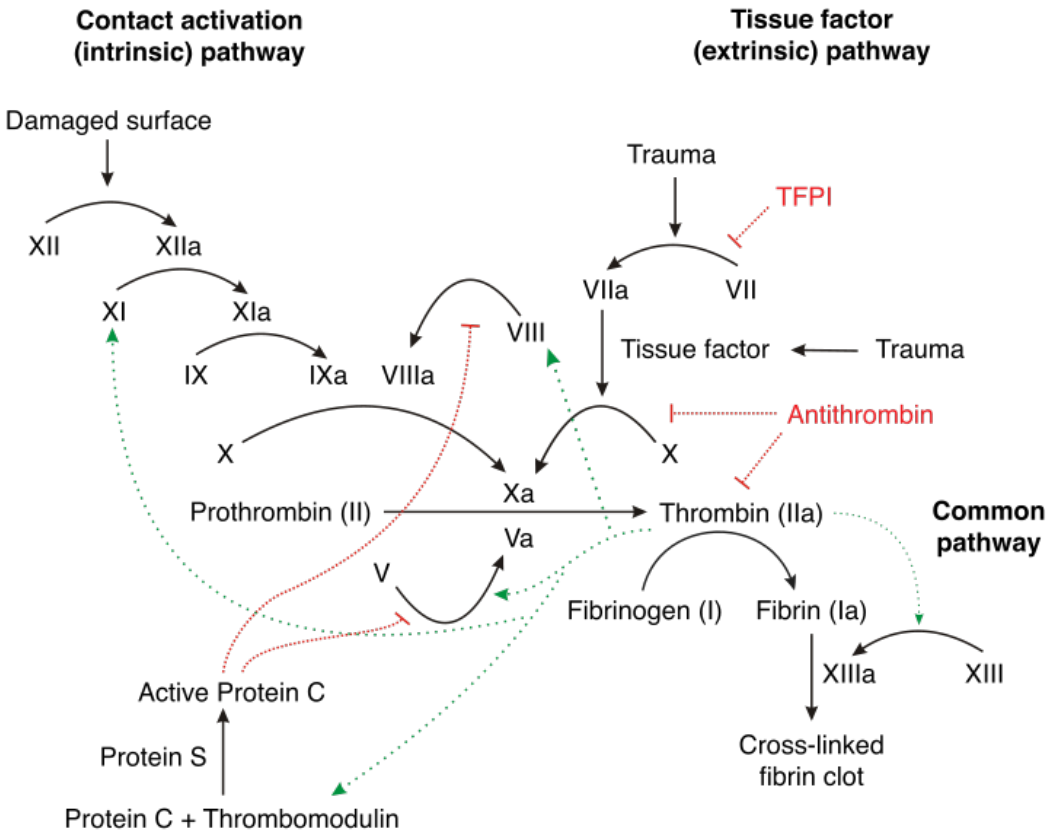


***Figure 5 - The coagulation cascade*[47]**

1.2.4.1.1 The intrinsic pathway

Endothelial damage exposes the sub-endothelium to blood, causing the activation of factor XII. This activation of factor XII in turn causes the activation of factor XI and subsequently factor IX in a cascade fashion. This cascade results in the activation of factor X, which combines with factor V to convert prothrombin to thrombin. Thrombin acts upon fibrinogen to create fibrin fibres, that form a loose mesh termed a *fibrin plug*.[42, 48]

1.2.4.1.2 The extrinsic pathway

Endothelial damage exposes the blood to tissue factor (TF), which combines with factor VII to activate factor X. This results in thrombin formation via the same mechanism described above.[48]

1.2.4.1.3 Platelet Activation

> Following activation, platelets undergo a change in morphology and secrete the contents of their granules. Activated platelets adhere at the sites of exposed collagen and form a platelet plug, strengthened by fibrin and von Willebrand factor, to arrest bleeding.[42]

The blood clot formed and the platelets contained within it act as a matrix for cell migration in the subsequent phases in the healing process. Platelet granules contain, amongst multiple other factors, platelet derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor and insulin-like growth factor, that act as promoters in the healing pathway by activating and attracting neutrophils, macrophages, endothelial cells and fibroblasts.[41]

1.2.4.2 Inflammation

The key aim of the inflammation phase is to prevent infection. Within the first hour following injury, and for the first 48 hours, the wound is infiltrated by highly motile neutrophils, mediated by the complement cascade in a process known as chemotaxis. Neutrophils have three main processes to dispose of foreign material, debris and bacteria[42, 44, 49]:

1. Phagocytosis, the direct ingestion of materials;
2. Degranulation, the release of toxins and proteolytic enzymes that destroy bacteria and dead host tissues;
3. Release of chromatin and protease 'traps' that capture and kill bacteria in the extracellular space.

Neutrophil activity gradually changes over the first 48 hours, and once bacteria have been removed, they either extrude to the wound surface and are removed as slough, or undergo apoptosis (programmed cell death). Cell remnants are then phagocytosed by macrophages.[41]

Between 48 and 72 hours following injury, macrophages enter the wound and continue the process of phagocytosis, attracted to the wound by chemoattractive agents. They have a longer lifespan and can function at a more acidic pH than

neutrophils.[41] Macrophages release a variety of growth factors into the wound that regulate the inflammatory response, stimulate angiogenesis and promote the formation of granulation tissue through the activation of keratinocytes, fibroblasts and endothelial cells.[41, 42, 50, 51]

The final cells to enter the wound in the inflammation phase are lymphocytes, that migrate to the area after 72 hours. They are attracted by the breakdown products of Interleukin-1 (IL-1), complement components and immunoglobulin G (IgG).[41] Evidence suggests they regulate wound healing through the production of an extracellular matrix scaffold and collagen remodelling.[42, 51, 52]

The inflammation process will continue as long as there is need for it, clearing bacteria and debris from the wound. Excessive or prolonged inflammation may lead to extensive tissue damage, delayed proliferation and, as a result lead to a chronic wound.[42]

1.2.4.3 Proliferation

Once haemostasis has been achieved, and the wound is free of debris, the proliferative phase of healing can commence. This phase begins on or around the third day post-injury and continues for around two weeks. It incorporates fibroblast migration, granulation, collagen deposition, angiogenesis, epithelialisation and wound retraction which occur simultaneously.[42, 53]

1.2.4.3.1 Angiogenesis

Angiogenesis takes place simultaneously during all phases of the wound healing process.[41] In response to hypoxia, vascular endothelial growth factor (VEGF) is released into the wound which, in combination with other cytokines, induce endothelial cells to trigger neovascularization and the repair of damaged blood vessels.[42] Initially the centre of the wound is avascular, so viable tissue is perfused by uninjured vessels and by diffusion through undamaged interstitium. Capillary sprouts from the surrounding edges invade the wound clot and, within a few days, a microvascular network composed of many new capillaries is formed.[41] Initially these capillaries are

fragile and permeable, contributing to the pink, fleshy appearance of granulation tissue that bleeds easily.[42]

1.2.4.3.2 Epithelialisation

Epithelial cells migrate from the edges of the wound soon after the initial insult. A single layer of cells forms over the entire wound in the initial phases, attaching to the matrix below. Once the entire wound is covered, migration stops and the basement membrane begins to form, prompted by a change in cytokine concentration. In wounds that are primarily closed, this process of re-epithelialisation may take as little as 24 hours.[41, 42]

1.2.4.3.3 Fibroblast Migration

Following injury, fibroblasts and myofibroblasts in the tissues surrounding the wound proliferate, before migrating into the wound from the third day onwards. Once in the wound, they produce the proteins making up the extracellular matrix, and subsequently collagen and fibronectin. At this point, the wound has a pink, fleshy appearance (granulation tissue). Once sufficient matrix has been laid down, fibroblasts change phenotype to become myofibroblasts, actively extending pseudopodia to connect to collagen and fibronectin. They subsequently actively contract to create wound contraction.[41, 42, 53]

1.2.4.3.4 Wound retraction

Wounds begin to contract about 7 days after injury, mediated mainly by myofibroblasts. Interactions between actin and myosin pull the cell bodies closer together decreasing the area of tissue needing to heal. Contraction can occur at a rate of 0.75 mm/day leading to shortened scars. Linear wounds contract fastest, and circular wounds the slowest.[42]

1.2.4.4 Remodelling

Remodelling is the final phase of wound healing, and may last up to two years. There is a delicate balance between synthesis and degradation of matrix within the wound, leading to increasing organisation of the collagens contained within it. Type 1 collagen becomes type 3, eventually regaining a structure similar to that seen in

unwounded tissue. Despite this, wounds never achieve the same level of tissue strength, on average reaching 50% of the original tensile strength by 3 months and only 80% long-term. As the scar matures, the level of vascularity decreases and the scar changes from red to pink to grey with time.[42]

1.2.5 Factors Impairing Wound Healing

Evidently, wound healing is a complex process with many stages involved. It stands to reason, therefore, that there are a number of factors, both within the patient and the environment, that may impair the healing of a wound. There is no one single factor that will predict a non-healing wound, but a combination of factors will make a chronic wound more likely. In general terms, these factors can be categorised into *local* and *systemic.*

1.2.5.1 Local Factors

1.2.5.1.1 Hypoxia

In the initial phases, wounds are relatively hypoxic, due to a disrupted blood supply and a high oxygen demand of metabolically active cells. Hypoxia can induce cytokine and growth factor production from macrophages, keratinocytes, and fibroblasts.[54] However, following this period of hypoxia, oxygen is required for the production of reactive oxygen species (ROS), produced by leukocytes for the process of oxidative destruction of bacteria. Similarly, it has been hypothesised that various growth factors, whilst initially stimulated by hypoxia, require oxygen for their continued production.[55] In summary, although hypoxia is important in the early wound healing phase, continued healing required adequate levels of oxygenation.[56, 57]

1.2.5.1.2 Infection

Injured skin loses the defence mechanisms normally in place to protect from infection, and so all wounds will be colonised with microorganisms. Infection can be split into either contamination or colonisation. Contamination is defined as the presence of non-replicating organisms within a wound, whereas colonisation can be defined as the presence of replicating microorganisms adherent to the wound but without causing tissue damage.

Colonisation alone does not delay the wound healing process. Local infection/ critical colonisation is an intermediate stage, with microorganism replication and the beginning of local tissue responses. Invasive infection is defined as the presence of replicating organisms within a wound with subsequent host injury.[56, 58] Bacteria are removed from the wound by the immune system during the inflammation phase of healing,[42] however a critical mass of bacteria may cause a prolongation of the inflammation phase, leading to a chronic, non-healing wound.[56] There is evidence to suggest, however, that sub- infective levels of bacteria appear to accelerate wound healing and formation of granulation tissue, with increased infiltrate of neutrophils, monocytes and macrophages, and an increase in collagen formation.[58]

1.2.5.2 Systemic Factors

1.2.5.2.1 Age

Increasing age is a major risk factor for impaired wound healing. This is associated with an altered inflammatory response, delayed re-epithelialisation, delayed collagen synthesis and delayed angiogenesis.[56, 59]

1.2.5.2.2 Nutrition

Nutrition has a significant impact on wound healing, which has been recognised by physicians for hundreds of years. Calorific value, carbohydrate, protein, fat, vitamin, and mineral metabolism can all affect the healing process.[57, 60, 61]

1.2.5.2.3 Diabetes Mellitus

Diabetes affected 422 million people worldwide in 2014 and the prevalence of the condition is predicted to continue to rise at an alarming rate.[62] Over 100 physiological factors have been shown to contribute to impaired wound healing in people with diabetes, including decreased or impaired growth factor production, angiogenic response, macrophage function, collagen accumulation, epidermal barrier function, quantity of granulation tissue, keratinocyte and fibroblast migration and proliferation, number of epidermal nerves and bone healing.[63, 64] Wounds in diabetics are also relatively more

hypoxic than wounds in non-diabetics, and the activity of reactive oxygen species is accelerated by both this hypoxia and hyperglycaemia.[56]

1.2.5.2.4 Medications

Many medications interfere with wound healing pathways. Glucocorticoids, such as prednisolone, are frequently prescribed in both primary and secondary care. They are well-known to inhibit wound repair via global anti-inflammatory effects and suppression of cellular wound responses, including fibroblast proliferation and collagen synthesis. On the other hand, topical low-dosage corticosteroid treatment of chronic wounds has been found to accelerate wound healing, reduce pain and exudate, and suppress hypergranulation tissue formation in 79% of cases.[56] Non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants, such as warfarin, have also been shown to impact the rate of wound healing.[57, 65]

1.2.5.2.5 Obesity

Obesity (defined as a Body Mass Index (BMI) ≥30) has been shown to have a significant impact on wound healing and wound infection rates[66, 67]. Complications may be attributable to a relative hypoperfusion of subcutaneous adipose tissue,[56] or to technical difficulties in operating on obese patients; operations taking more time, thus increasing the chances of contamination; more trauma; and even necrosis of the abdominal wall because of more forceful retraction during surgery.[68] Poor tissue oxygenation and increased wound tension may also account for a higher rate of wound dehiscence in those that are obese.[68]

1.2.5.2.6 Smoking

Post-operatively, patients who smoke show a delay in wound healing and an increase in a variety of complications such as infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and a decrease in the tensile strength of wounds.[56, 69] A variety of clinical trials have shown that those who smoke have poorer outcomes following surgery compared to those that do not smoke. One review of 916 skin flaps and grafts concluded

that smokers of more than one pack per day were three times more likely to develop skin necrosis.[70] Tissue hypoxia has been regarded as a major mechanism for tobacco-related impairment of wound healing. Ten minutes of smoking can decrease tissue oxygen concentration for as long as 1 hour. This implies that smokers who consume 1 pack of cigarettes a day would live under tissue hypoxia throughout the day. Nicotine has also been shown to have vasoconstrictive effects at the dermis, and cigarette smoking has been shown to have a negative influence on fibroblastic activity, epithelialization, and immune response.[71, 72]

1.3 Surgical Site Infection

1.3.1 Terminology and Definition

The Centres for Disease Control and Prevention (CDC) defines a surgical site infection (SSI) as an infection taking place at the site of surgery within 30 days of that surgery, or within 90 days if a prosthesis is left in place, affecting either the superficial incised tissues, the deep tissues or the deep organ space (Figure 6).[73, 74]

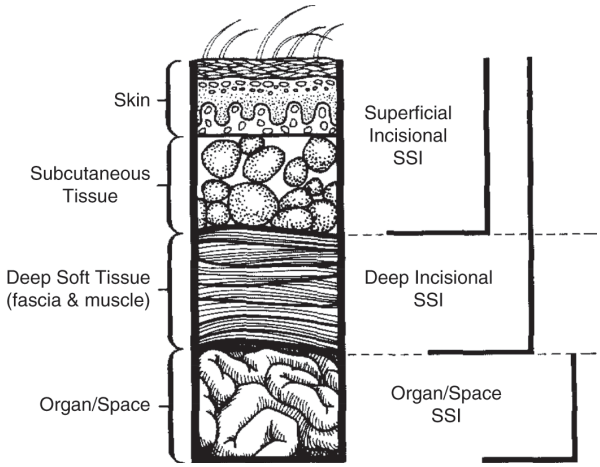


Figure 6 - Anatomical classification of SSI[2]

1.3.2 Epidemiology

SSI account for up to 20% of all healthcare acquired infections and occur in up to 5% of all procedures undertaken.[75] SSI rates vary by operation site, type, and contamination. Procedures can be classified by type, into clean; clean-contaminated; contaminated; and dirty, in relation to the potential for surgical site infection (Table 1).

Table 1 – Wound Classification. Adapted from Culver et al[76] and Ortega et al[77]

Wound Classification	Description	Infective Risk (%)
Clean	Uninfected operative wound, No acute inflammation, No entry to internal organs, No break in aseptic technique, Typically elective, E.g. hernia repair	1.8 – 2.1%
Clean-Contaminated	Opening to internal organ but minimal or no spillage of contents, No evidence of infection or major break in aseptic technique, E.g. appendicectomy.	3.3 – 3.9%
Contaminated	Opening to internal organs with inflammation or spillage of contents, Major break in aseptic technique Presence of acute non-purulent inflammation, E.g. colectomy for obstruction.	4.8 – 6.4%
Dirty	Purulent inflammation present, Presence of devitalised tissue, Intraperitoneal abscess formation or visceral perforation E.g. Wound debridement, laparotomy for bowel perforation.	5.2 – 7.1%

Despite advances in prevention and treatment, the burden of SSI remains high. Between 1 in 7 and 1 in 5 hospital acquired infections in the United Kingdom (UK) are SSIs.[78] Patients with SSI have long unplanned hospital stays, are five times more likely to be readmitted after discharge, are 60% more likely to spend time in an intensive care unit (ICU), and twice as likely to die as those without SSI.[79-81]

As well as a significant cost to the patient, SSI cause an increase in cost to the National Health Service (NHS). The average increase in hospital stay in patients who develop SSI is 10 days, and costs to the NHS have been estimated between £3000 and £6000 per patient per SSI.[78] This amounts to a cost of £700 million per annum to the NHS.[79] Costs are not only attributed to increased length of stay, but also to investigation, management and reintervention.[82]

Reported infection rates are also likely to be an underestimation of true rates of SSI. Tanner *et al* examined the rates of SSI following colorectal surgery, comparing their findings to nationally reported surveillance data. They found an SSI rate of 27%, in comparison to a reported rate of 16%, suggesting that around 40% of SSI may go unreported.[83] This underreporting of SSI also leads to an underreporting of cost, meaning that the true burden of SSI in the UK is unknown.

Within vascular surgery, there is huge variation and probably gross underreporting of SSI rates. For example, SSI rates following open varicose vein surgery have been reported between 1.5% and 24%[84, 85] and figures from SSI surveillance demonstrated a high rate of SSI in patients undergoing lower limb amputation (13.1%).[86] In one study, infection rates following major lower limb amputation were found to be as high as 22.5%.[87] A large study of trends in vascular surgery estimated an infection rate of just over 3%[88] in lower limb revascularisation surgery, however a randomised controlled trial carried out in 2012 found an overall SSI rate of 22.1% after the same procedures.[89]

Overall, this higher than expected rate of SSI in patients undergoing vascular surgery may, in part, be due to an increased number of co-morbid conditions. The prevalence of diabetes in patients undergoing major amputations has been estimated at 65.95%, and around 40% in lower limb revascularisation surgery.[88]

One area that goes against this trend, however is in carotid surgery; infection following carotid endarterectomy (CEA) is generally low, with studies identifying infection rates between 0.2% and 0.8%.[90-92]

1.3.3 Clinical Presentation

Clinical signs and symptoms of a wound infection may include increased redness, pain, head, swelling related to the incision and wound exudates, which may be characteristic in their appearance or colour, including the drainage of pus.[58, 75]

1.3.4 SIRS and Sepsis Syndrome

Systemic inflammatory response syndrome (SIRS) and sepsis are potential sequela of wound infections. SIRS is the presence of more than one of: Body temperature >38°C or <36°C; tachycardia (heart rate >90 beats per minute); tachypnoea (respiratory rate ≥20 breaths per minute); and a white blood cell count (WCC) $>12x10^9$ or $<4x10^9$. When SIRS is the result of an infective process, this is termed sepsis. A frequent complication of SIRS is the development of organ system dysfunction, including such well-defined clinical conditions as acute lung injury, shock, renal failure, and multiple organ dysfunction syndrome (MODS).[93]

1.3.5 Risk Factors for Developing a Surgical Site Infection

There are a number of factors that may increase the risk of developing SSI following vascular surgery (Table 2).

Table 2 – Surgery and patient related risk factors for SSI in Vascular Surgery[94]

Surgery Related	Patient Related
Delayed surgery	Advanced age
Long procedure	Renal insufficiency
Presence of a groin incision	Diabetes
Post-operative seroma or haematoma	Distal skin necrosis or gangrene
're-do' surgery	Female gender
Undermining skin edges	Malnutrition
Use of prosthetic graft material	Obesity
	Pre-operative use of aspirin
	Rest pain

An extensive systematic review of 57 studies characterised the risk factors associated with SSI,[95] finding that co-morbidities were consistently associated with SSI, the most common being diabetes mellitus. If a patient has multiple co-morbidities this was associated with an estimated odds ratio for SSI 6.1 [95% CI: 1.3-28.9] in all major surgeries.[95] Other factors that have been associated with an increased risk of SSI include an American Society of Anaesthesiologists (ASA) score of greater than or equal to 2 (see table 3, below); having a contaminated or dirty wound; and a longer operative procedure.[94, 96-98]

Table 3 – ASA grading system. Adapted from Daabiss, 2011[99]

ASA Grade	Description
I	Patient is a completely healthy, fit patient
II	Patient has mild systemic disease
III	Patient has severe systemic disease that is not incapacitating
IV	Patient has incapacitating disease that is a constant threat to life
V	A moribund patient who is not expected to live 24 hours with or without surgery

1.3.6 Recommendations for Reducing Surgical Site Infection

SSI carry significant morbidity and mortality, and have a significant impact on patients.[100] Their prevention is of paramount importance to those involved in the care of surgical patients, and to the patients themselves. Consequently, the World Health Organisation (WHO) and the National Institute for Health and Care Excellence (NICE) have each published extensive guidelines on the reduction of the risk of SSI in patients undergoing surgery. Both organisations divide their recommendations by the point in time at which they are implemented: *preoperative, intraoperative* and *postoperative.*

1.3.6.1 Preoperative measures for reducing SSI

1.3.6.1.1 Perioperative discontinuation of immunosuppressant medication

The WHO recommends against stopping immunosuppressant medication, as this may cause a flare of the underlying disease, which may in turn be associated with poor outcomes.[101] NICE does not have any recommendations for the cessation of immunosuppressant medications.

1.3.6.1.2 Nutritional support

Both WHO and NICE recommend that patients who are scheduled to undergo surgery who are underweight or malnourished should be considered for oral or enteral multiple nutrient-enhanced nutritional formulas. Early nutritional

support has been associated with an improvement in outcome and a reduction in infective complications following surgery.[101, 102]

1.3.6.1.3 Pre-operative bathing

Both the WHO and NICE recommend that patients shower or bathe using plain or antimicrobial soap either the day before, or on the day of, surgery.[75, 101] There was insufficient evidence across seven RCTs and two observational studies to suggest that antimicrobial soap was associated with any reduction of infection rates over plain soap.[101]

1.3.6.1.4 Nasal Decontamination

Patients who are known nasal carriers of *S. aureus* can undergo decontamination with 2% mupirocin ointment intranasally, in combination with a body wash containing chlorhexidine gluconate, a bactericidal antiseptic, pre-operatively. NICE and the WHO provide differing recommendations when considering decontamination. NICE recommends against the routine decontamination of patients undergoing surgery,[75] whereas the WHO recommends this practice in those undergoing cardiothoracic and orthopaedic surgery, and may recommend it for other surgical specialties.[101]

1.3.6.1.5 Hair Removal

Hair removal should be avoided in order to reduce the risk of SSI, as it is believed to cause microtrauma to the skin leading to the ingress of bacteria. If hair removal is required, this should be performed with clippers with a single-use head on the day of surgery. The use of razors to shave the area is associated with an increased risk of SSI.[75, 101]

1.3.6.1.6 Antibiotic Prophylaxis

Both organisations have recommendations on the use of antibiotic prophylaxis prior to surgery. Prophylaxis should be given to patients undergoing clean surgery involving an implant, clean contaminated or contaminated surgery.[75] Prophylaxis should be delivered within 120 minutes of the skin incision, considering the half-life of the agent to be used, which

should be chosen in line with the local antibiotic formulary.[101] A repeat dose should be given where the operation lasts longer than the half-life of the chosen agent.[75]

1.3.6.1.7 Preparation of the Surgeon

Surgeons and theatre staff should wear specific, non-sterile theatre-wear when in the operating theatre. Surgeons should remove hand jewellery and artificial nails prior to any procedure.[75] Surgeons should decontaminate their hands either by scrubbing with a suitable antimicrobial soap and water or using a suitable alcohol-based hand rub before donning sterile gloves.[101]

1.3.6.2 Intraoperative measures for reducing SSI

1.3.6.2.1 Antiseptic skin preparation

Skin should be prepared immediately before the incision (giving enough time for alcohol-based solutions to dry completely if diathermy is to be used).[75] Alcohol-based solutions have been shown to be more effective at reducing SSI than aqueous solutions, with chlorhexidine-containing preparations shown to be superior to povidone-iodine based preparations in a meta-analysis of 12 RCTs.[101]

1.3.6.2.2 Perioperative Oxygenation

Patients should be given 80% inspired oxygen throughout the procedure, and for 2-6 hours post-operatively, as this has been shown to reduce the risk of SSI.[103] Oxygen should be delivered to maintain a haemoglobin oxygen saturation (SpO_2) of >95%.[75]

1.3.6.2.3 Patient body temperature

Body warming, in order to avoid a body temperature of <36°C, has been shown to reduce the risk of SSI in two RCTs, and temperature should be maintained throughout the procedure. [75, 101]

1.3.6.2.4 Maintaining patient blood glucose levels

Recommendations regarding the control of blood glucose vary between the two organisations. NICE recommends against the use of insulin in non-

diabetics[75] however the WHO recommends the use of protocols for intensive perioperative management of blood glucose levels.[103] They do not, however, define the use of insulin in protocols. It is agreed that strict glucose control is necessary intraoperatively.

1.3.6.2.5 Maintaining circulating volume

Perfusion should be maintained using goal-directed fluid therapy to maintain circulating volume. A meta-analysis of 14 RCTs showed that intraoperative goal directed fluid therapy was significantly associated with lower incidence of SSIs than standard intraoperative fluid management (OR 0·56; 95% CI 0.35–0.88).[75, 101]

1.3.6.2.6 Drapes and gowns

Gowns, surgical drapes and adhesive plastic incise drapes, with or without antimicrobial impregnation, are available for use. Sterile disposable non-woven or sterile reusable woven drapes and surgical gowns should be used during surgical operations for the purpose of preventing SSI. Plastic adhesive incise drapes with or without antimicrobial properties should not be used.[75, 101]

1.3.6.2.7 Wound irrigation

Although NICE recommends against the irrigation of a wound prior to skin closure,[75] the WHO recommends the use of irrigation of the incisional wound with an aqueous povidone-iodine solution, particularly in clean or clean-contaminated surgery, as this reduces the risk of SSI.[103]

1.3.6.2.8 Prophylactic negative pressure wound therapy

Negative pressure wound therapy (NPWT) consists of a closed sealed system connected to a vacuum pump, which maintains negative pressure on the wound surface. The WHO recommends the use of NPWT as prophylaxis against SSI in 'high risk' primarily-closed wounds (such as poor tissue perfusion due to surrounding soft tissue or skin damage, decreased blood flow, bleeding or haematoma, dead space, or intraoperative contamination).[103] NICE offer no specific recommendations for the use of

NPWT for primary prevention of SSI. A 2014 Cochrane Review of 9 RCTs found limited evidence for the use of NPWT in primarily healing wounds.[104]

1.3.6.2.9 Wound dressings

NICE recommends that wounds are covered with an appropriate dressing at the end of a procedure.[75] The WHO recommend a standard dressing rather than an advanced dressing on primarily closed surgical wounds for the purpose of preventing SSIs, although acknowledge that this is based on low quality evidence.[103]

1.3.6.3 Postoperative measures for reducing SSI

1.3.6.3.1 Postoperative antibiotic prophylaxis

The WHO outlines in their guideline that there is poor evidence to suggest prolonged courses of postoperative antibiotics are beneficial in reducing SSI. A single post-operative dose may be non-inferior to 24 hours of antibiotics. They therefore recommend the use of antibiotics immediately post-operatively, but advise against prolonged use.[103]

1.3.7 Microbiology

All wounds will be colonised with bacteria – that is they will contain non-replicating bacteria that do not cause infection. Wounds become locally infected once they are 'critically colonised.' Wound infection can be defined as the presence of replicating organisms within a wound with subsequent host injury.[58] Causative organisms are varied, with a number of different studies quantifying organisms seen in SSI. Most pathogens originate from the patient's own skin flora. The most commonly isolated organisms are *Staphylococcus aureus (S. aureus)*, coagulase-negative staphylococci, *Enterococcus species* and *Escherichia coli*.[105] One retrospective study of over 600 abdominal SSI isolated *S. aureus* (28.2%) and *Pseudomonas aeruginosa* (25.2%), and found polymicrobial infection in 343 of their 614 cases.[106] A large population study of 8302 patients in the USA found that *S. aureus* accounted for 46% of the SSIs they identified.[107]

Both studies above identified an increase in antibiotic resistant pathogens, predominantly methicillin-resistant *S. aureus* (MRSA), with one study finding that MRSA isolation increased from 11.5% in 2003 to 16.0% in 2006.[107] This increase may be a reflection of the increased use of broad spectrum antibiotics and the increased prevalence of MRSA in skin flora.[105] Patient outcomes are less favourable with a MRSA SSI compared to methicillin-sensitive *S. aureus* (MSSA) infection, with an increase in both 30-day mortality and morbidity.[108]

SSI in vascular surgery is of particular concern due to the involvement of materials such as prosthetic grafts. Graft infection is uncommon, occurring at rates between 0.1% and 3.1%, however when they do occur are a significant cause of morbidity and mortality. Historically, the most common pathogen found in early onset infections were coagulase-positive staphylococci, such as *S. aureus*, and in late-onset infections coagulase negative staphylococci such as *S. epidermidis* were most common.[94] *S. aureus* and *S. epidermidis*, together with *Escherichia coli* make up around 75% of early and late graft infections.[109]

1.3.8 Outcome Measures in Infection

There are a number of different outcome measures in SSI, with one review identifying 41 definitions and 13 grading scales used in 82 studies.[110] However, the CDC published the following guidelines defining superficial and deep incisional SSIs.[73]

1.3.8.1 Centres for Disease Control and Prevention (CDC) definition

The CDC defines surgical site infection according to the anatomical location of the infection.

1.3.8.1.1 Superficial incisional SSI

A superficial incisional SSI must meet the following criteria[74]:

- Infection occurs within 30 days of the operative procedure **AND**
- Involves only the skin and/or the subcutaneous tissues **AND**
- The patient has at least *one* of the following:
    - purulent drainage from the superficial incision

- organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture
- Superficial incision that is deliberately opened by a surgeon, attending physician or other designee and culture or non-culture based testing is not performed **AND** patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat.
- diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.

1.3.8.1.2 Deep incisional SSI

A deep incisional SSI must meet the following criteria[74]:

- Infection occurs within 30 days (or 90 days if a prosthetic implant is used) of the index procedure **AND**
- Involves deep soft tissues of the incision (e.g., fascial and muscle layers) **AND**
- The patient has at least *one* of the following:
  - purulent drainage from the deep incision
  - a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician or other designee and organism is identified by a culture, or culture is not performed **AND** patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness
  - an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

1.3.8.1.3 Organ Space SSI

An organ space SSI must meet the following criteria[74]:

- Infection occurs within 30 days (or 90 days if a prosthetic implant is used) of the index procedure **AND**
- Infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure **AND**

- The patient has at least *one* of the following:
    - Purulent drainage from a drain that is placed into the organ/space (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)
    - Organisms are identified from an aseptically-obtained fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method
    - an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.

1.3.8.2 ASEPSIS Score (Table 4)

ASEPSIS is a quantitative measure of scoring a wound that provides a numerical score. The overall score is related to the severity of wound infection using objective criteria based on appearance and the clinical consequences of the infection.[111, 112] ASEPSIS has been reported to be repeatable and related to patient outcome.[113, 114]

Table 4 – The ASEPSIS scoring system[112]

	Score
Wound Characteristic	
Serous exudate	3
Erythema	3
Purulent exudate	6
Separation of wound edges	6
Additional Treatment	
Postoperative antibiotics	10
Abscess drainage	5
Wound debridement	10
Isolation of bacteria	10
Prolonged stay/readmission to hospital	5

A score of 21 or more is indicative of the presence of infection (SSI). A score between 10 and 21 indicates impaired wound healing (IWH). A score below 10 indicates satisfactory wound healing.

It has been shown that there is disparity between assessment/definition methods, with a poor agreement between the CDC definition and ASEPSIS score for individual wounds.[115]

1.3.8.3 Public Health England Surveillance Questionnaire

In order to capture data on SSI post-discharge, Public Health England (PHE) adapted the CDC criteria and ASEPSIS tools to produce a surveillance questionnaire.[116] This is available for patient completion, although it has not been formally validated.[117]

1.3.8.4 Quality of Life Outcome Measures

Health related quality of life (QoL) instruments are designed to provide a holistic view of the health of the individual across a number of domains, including physical, emotional and mental wellbeing. Surgical site infection has been shown to adversely affect QoL.[118]

1.3.8.4.1 Short-Form 36 Questionnaire (SF-36)

The short-form 36 (SF-36) QoL instrument contains thirty-six questions that generates a health profile. It is split into eight domains: physical function (PF), role limitation due to physical state (RF), general health (GH), vitality (VT), bodily pain (BP), social function (SF), mental health (MH) and role limitation due to emotional state (RE).[119] The domains are recorded on a scale of 0 to 100, where 0 is worst possible health and 100 is the best possible health. The domains can be grouped together produce a mental component score (MCS) and physical component score (PCS). The SF-36 is the most widely used questionnaire for all disease groups and populations.

1.3.8.4.2 EQ-5D-3L

The EQ-5D is a generic instrument for describing and valuing health. It is based on a descriptive system that defines health over 3 levels in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression.[120] It

was updated in 2011 to a 5 level questionnaire.[121] It is a widely recognised and validated generic measure of health related QoL. This questionnaire has been assessed for acceptability and validity in a number of patient groups.[122, 123]

1.4 Wound Dressings

Although most wounds heal uneventfully, the management of more complex wounds requires a multi-disciplinary approach, including input from specialist services such as tissue viability services. Good quality randomized controlled trials in wound care are scarce, with the result that clinical guidelines are largely based on expert opinion.[124] One reason for this is the heterogeneous nature of this patient population. As a result, there are a large number of therapies available and an absence of an agreed gold standard of care.[125]

Since the 1960's, occlusive wound dressings have aimed to retain moisture in the wound, after a moist wound environment was found to significantly improve epithelialisation rates.[34] Occlusive dressings may also reduce SSI rates.[126]

1.4.1 The Ideal Wound Dressing

A physiological wound environment is achieved when a dressing does the following:

- Keeps the wound moist;
- Absorbs excess exudate without wound leakage;
- Provides thermal insulation, keeping the wound environment at a temperature similar to body temperature;
- Eliminates 'dead' space;
- Avoids pain or trauma when changing the dressing;
- Is non, or minimally-toxic to the wound and the surrounding tissues;
- Minimises the formation of scar tissue;
- Debrides non-viable tissues;
- Allows for the maintenance of gas exchange.

1.4.2 Wound Dressings by Type

Dressing products have evolved significantly in the past decades, and now fall into broad, widely-recognised categories[127]:

1. Basic wound contact layers, such as gauze or cotton absorbents
2. 'Advanced' dressings such as hydrogels, hydrocolloids and films
3. Anti-microbial and other specialist dressings.

Within these groups there are many hundreds of dressing types available. In addition, a 'fourth' category may be considered, that of 'wound exposure' – leaving a wound dressing free. In some cases, wounds healing by primary intention following surgery may be left uncovered.

1.4.2.1 Basic Wound Contact Layers

1.4.2.1.1 Absorbent dressings

Absorbent dressings are applied directly to the wound. They are not suitable for application to heavily exuding wounds.[127, 128]

1.4.2.1.2 Low adherence dressings

Low adherence dressings and wound contact materials are usually cotton pads that are placed directly in contact with the wound. They are usually made of a fine, woven mesh which allows exudates to pass through.[125] They are either non-medicated (e.g. paraffin gauze dressing), or medicated (e.g. containing povidone iodine or chlorhexidine).[128]

1.4.2.2 Advanced Wound Dressings

1.4.2.2.1 Hydrogel dressings

Hydrogel dressings are most commonly supplied as a topical application that can take up the shape of a wound. These dressings are generally used to donate liquid to dry sloughy wounds and facilitate autolytic debridement of necrotic tissue; some also have the ability to absorb very small amounts of exudate. A secondary, non-absorbent dressing is needed to cover the area[125, 127]

1.4.2.2.2 Vapour-permeable films and membranes

Vapour-permeable films are permeable to water vapour and oxygen, but not to water or micro-organisms.[128] They consist of a thin, polyurethane-type film coated with an adhesive layer enabling the dressing to adhere to intact skin. Film dressings provide a protective environment that is impermeable to bacteria and liquids and can stay in place for up to 7 days. They are indicated for dry, superficial wounds as a primary dressing however can be used as a secondary dressing on top of dressing pads or foam dressings in heavier exuding wounds.[125] They are highly conformable, provide protection, and a moist healing environment, and transparent film dressings permit constant observation of the wound.[127]

1.4.2.2.3 Hydrocolloid dressings

Hydrocolloid dressings are occlusive dressings that form a gel in the presence of wound exudate. In lightly to moderately exuding wounds, they promote autolytic debridement of dry, sloughy, or necrotic tissue.[127] Fibrous hydrocolloid dressings work in a similar fashion, but are more suited to heavily exudative wounds.[127, 128]

1.4.2.2.4 Foam dressings

Foam dressings are made of polyurethane or silicone, enabling them to handle large volumes of exudate. They are available in various thicknesses in adhesive and non-adhesive formulations.[125] Foam dressings can be used in combination with other primary wound contact dressings, and may also be used to provide a protective cushion for fragile skin.[127]

1.4.2.2.5 Alginate dressings

Alginate dressings are made from calcium alginate, or calcium sodium alginate, which is derived from brown seaweed. They form a soft gel in contact with wound exudate. Alginate dressings are highly absorbent and suitable for use on exuding wounds, and for the promotion of autolytic debridement of debris in very moist wounds. Alginate dressings also act as a haemostatic agent. Alginate sheets are suitable for use as a wound contact dressing for moderately to heavily exuding wounds and can be layered into deep wounds; alginate rope can be used in sinus and cavity wounds to improve absorption of exudate and prevent maceration.[125, 127]

1.4.2.3 Antimicrobial Dressings

1.4.2.3.1 Honey

Medical grade honey has antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Medical grade honey has osmotic properties, producing an environment that promotes autolytic debridement.[127] It has been suggested as a treatment in resistant organism infection.[15] Medical grade honey is available as a topical application, or as a sheet dressing for covering wounds.[127]

1.4.2.3.2 Iodine

Iodine-containing dressings release free iodine into the wound, which acts as an antiseptic at the wound surface. Iodine has a wide spectrum of antimicrobial activity but it is rapidly deactivated by wound exudate.[127] It reduces the microbial load of a wound, reducing the risk of infection.[129]

1.4.2.3.3 Silver

Silver, in ionic or nanocrystalline form, has for many years been used as an antimicrobial agent, particularly in the treatment of burns.[129] Silver ions exert an antimicrobial effect in the presence of wound exudate. Dressings impregnated with silver sulfadiazine have a broad antimicrobial activity.[127]

1.4.2.3.4 Other antimicrobials

Dressings may contain chlorhexidine acetate, a bactericidal or bacteriostatic antiseptic that disrupts the cell membranes of bacteria,[130] or polyhexamethylene biguanide (PHMB), a synthetic antimicrobial peptide that destroys bacteria. These are available for the use on infected wounds.[127]

1.4.2.4 Complex and Adjunctive Therapies

1.4.2.4.1 Larval therapy

Larval therapy has been used in wounds for centuries. Larvae offer the benefit of eliminating bacteria from the wound through ingestion and degradation. They are effective at debriding slough or stable haematoma from a wound where surgical debridement may not be an option.[125] Larval therapy offers numerous advantages

including rapid wound debridement and elimination of infection, control of pain and odour, and the promotion of wound healing.[131]

1.4.2.4.2 Negative pressure wound therapy

NPWT assists wound closure by applying localized negative pressure to a wound to promote wound contraction, angiogenesis and removal of excess fluid. Foam or gauze is inserted into open wounds and covered with a film drape, then negative pressure is applied by means of a pump system.[125] Although the evidence for its use is low quality, it does suggest that the effectiveness of NPWT is at least as good as or better than conventional treatment for open wounds.[132]

1.4.3 Dressings for the Prevention of Surgical Site Infection

A Cochrane review into the use of dressings in the prevention of SSI was published in 2011,[133] with updates in 2014[128] and 2016.[134] In the most recent review, 29 trials (5718 patients) were identified and included. Four trials compared wound dressings with no wound dressing (wound exposure); the remaining 25 studies compared alternative dressing types. The majority of studies compared a basic wound contact dressing with film dressings, i.e. silver dressings or hydrocolloid dressings. Of the 29 included trials, only a single study was deemed to be at a low risk of bias, with fourteen studies judged to be at a high risk of bias across more than one domain.[134] This limits the usefulness of the review, outlining the need for further, high quality evidence which minimises the risk of bias, examining the use of dressings in reducing SSI.

The authors concluded that there is currently insufficient evidence to determine whether covering surgical wounds that are healing by primary intention with wound dressings reduces the risk of SSI, or whether any particular type of wound dressing reduces the risk of SSI more than another. They also comment that there is a lack of high quality research evidence regarding whether choice of wound dressing (or indeed use of wound dressings at all) affects the risk of SSIs in people whose surgical wounds are healing by primary intention.[134]

1.5 Cell Surface Hydrophobicity

In order to understand wound infection, and to develop effective methods of preventing and treating them, it is important to understand the characteristics of pathogenic bacteria. An understanding of these characteristics allows the targeted development of devices, such as wound dressings, to prevent wound infections.

The most common organisms causing wound infections are *S. aureus* and *Pseudomonas aeruginosa.*[106] Organisms have a number of properties that impact their virulence. Amongst these virulence factors is the expression of surface molecules with a high cell surface hydrophobicity (CSH).[135] Microbial cell surface proteins mediate binding to extracellular matrix (ECM) proteins such as fibronectin and collagen, and plasma proteins, such as fibrinogen, by receptor-specific interaction. This binding leads to adhesion to host tissue, which may lead to infection.[136]

The hydrophobic effect is one of the mechanisms by which bacteria adhere to both each other and to tissues, and there is a clear correlation between hydrophobicity and infection.[137] Virulent microbes express cell surface molecules with a high CSH, leading to the process of hydrophobic interaction. Two hydrophobic molecules expel the water molecules contained between them, causing them to 'stick,' and remain held together by the now surrounding water molecules (Figure 7).[1, 138]

A number of pathogenic bacteria have been shown to express varying levels of hydrophobicity (Table 5).[137]

Table 5 – Hydrophobic properties of pathogenic microorganisms, adapted from Doyle (2000)[137]

Pathogen	**Observations**
Acinetobacter baumannii	Lower respiratory tract isolates tended to be highly hydrophobic
Aeromonas hydrophila	Virulence of human isolates was correlated with hydrophobicity
	Virulence of human isolates was correlated with hydrophobicity
Campylobacter jejuni	High negative surface charge, in combination with hydrophobicity, seemed to promote adhesion to tissue culture cells
Escherichia coli	Most enteropathogenic isolates were hydrophobic
Peptostreptococcus micros and *Streptococcus mitis*	High levels of hydrophobicities were determined
Staphylococcus aureus	Bovine mastitis strains expressed hydrophobic surface regardless of growth medium
Streptococcus pyogenes	Many clinical isolates were hydrophobic
Vibrio spp.	Pathogenic members of the genus Vibrio were highly hydrophobic
Candida albicans	A strong correlation was shown between adhesion to buccal cells and hydrophobicity

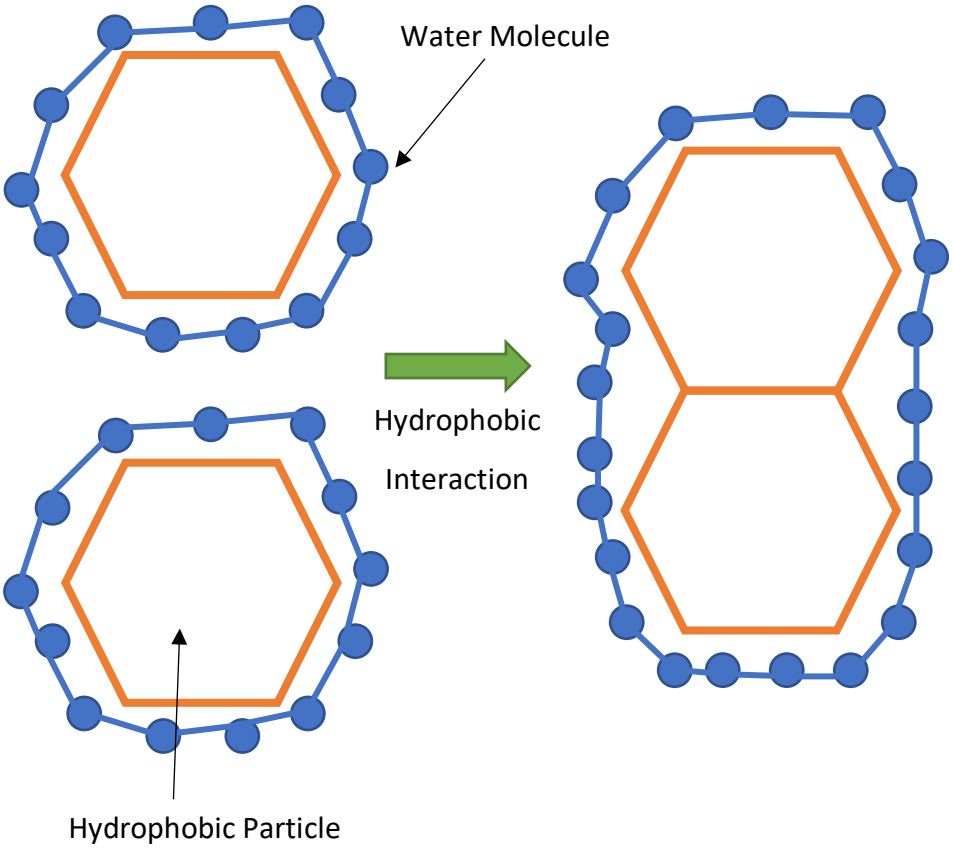


Figure 7 - Hydrophobic Interaction (adapted from Butcher (2011)[1])

1.6 Dialkylcarbamoylchloride

Using the principles of hydrophobic interaction, microorganisms expressing a high level of CSH may be removed from the wound by a hydrophobic material introduced to the area in the form of a dressing.[136] Dialkylcarbamoylchloride (DACC) is a synthetically manufactured derivative of a fatty acid found naturally in cobwebs. Cobwebs have been used as a wound covering since ancient times, used as both a haemostat and to treat infection.[139] When used as a wound covering, microorganisms with a hydrophobic cell surface are irreversibly bound to the DACC-coating by hydrophobic interaction. Once bound to the dressing, bacteria and fungi are rendered inert and so are prevented from multiplying or releasing toxins. At each dressing change, microorganisms are then removed from the wound bed along with the dressing.[1]

1.6.1 Laboratory Evidence

DACC-technology has been the subject of clinical and lab-based investigation for some time. In some of the earliest work, hydrophobic dressings were superior to other dressings in reducing infections from common pathogens in superficial wounds.[140] Hydrophobic dressings are more effective in binding bacterial species than alginate dressings, binding particularly high proportions of *Pseudomonas aeruginosa*.[141]

In 2006, *in vitro* studies showed that *S. aureus* and *Psuedomonas aeruginosa* bound strongly to the DACC-dressing, reaching a peak at 120 minutes following exposure.[136] Bacterial counts then remained stable up to 20 hours following exposure, suggesting that microbes multiply to a very low extent following binding.

Mycobacterium ulcerans, responsible for Buruli ulceration of the lower limb, has been shown to bind strongly to DACC-coated dressings.[142] In addition, DACC-coated dressings are capable of binding both MRSA and MSSA with similar efficacies.[143] MRSA biofilms have since been demonstrated to bind to DACC-coated dressings with greater affinity than to conventional dressing material.[144] This evidence is the first to suggest that DACC-coated dressing materials may be effective against drug-resistant pathogens.

1.6.2 Clinical Evidence

Clinical evidence in favour of the use of DACC-coated dressings remains limited. DACC-coated dressings were not studied in the Cochrane review.[134] Therefore, the first aim of this thesis was to undertake a systematic review of the literature into the use of DACC-coated dressings in the treatment or prevention of wound infection.

CHAPTER 2: STUDY ONE – A SYSTEMATIC REVIEW OF THE USE OF DIALKYLCARBOMOYLCHLORIDE- COATED DRESSINGS IN THE MANAGEMENT AND PREVENTION OF WOUND INFECTION

2.1 Objectives

Despite a large range of wound dressings, current evidence suggests that no particular dressing significantly impacts wound infection incidence or outcomes.[134] The first study of this thesis, therefore, was a systematic review of the existing literature examining the use of DACC-coated dressings in wound management; either the prevention of infection in wounds healing by primary or secondary intention, or in the treatment of wounds already showing signs of local or systemic wound infection. The aim or this study, therefore, was to identify the current available evidence supporting the clinical use of DACC-coated dressings in managing or preventing wound infections.

2.2 Methods

2.2.1 Criteria for Considering Studies for the Review

All studies investigating the role of DACC coated dressings in wound care, with primary or secondary outcomes related to infection, were considered for inclusion. We included both randomised and non-randomised trials, cohort studies and case series. Only full text reports regarding human subjects and in the English language were included.

Studies were excluded if the report was regarding an in-vitro or basic science study exploring the mode of action of DACC coatings. In addition, we excluded papers if DACC was used in conjunction with other advanced dressing systems, or the article was a case series with less than three cases.

2.2.2 Search Strategy

This systematic review was undertaken in line with recommendations from the PRISMA statement.[145] Medline, Embase, CENTRAL and CINAHL databases were searched from 1946 to September 2016. The full search strategy used is given in tables 6-8. Additional articles were sourced by hand searching the reference lists of relevant articles and via a Google scholar search.

Table 6 - Search Strategy: Embase 1974 to 2016 September 13 and Ovid MEDLINE 1946 to September 2016

Search	Terms	Results
1	Dialkylcarbamoylchloride.mp	3
2	Dialkylcarbamoyl chloride.mp	5
3	Dialkyl carbamoyl chloride.mp	13
4	DACC.mp	1063
5	leukomed.mp	5
6	cutimed.mp	45
7	sorbact.mp	58
8	hydrophob*.mp	240177
9	dressing.mp	38498
10	8 and 9	179
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 10	1281
12	infect*.mp	4099272
13	wound*.mp	619850
14	surg*.mp	4422074
15	ulcer*.mp	538117
16	12 or 13 or 14 or 15	8790031
17	11 and 16	259
18	limit 17 to human	158
19	limit 18 to English language	150

*Search terms all mapped to subject headings. * is used as a wildcard operator in the search.*

Table 7 – Search Strategy: CINAHL via EBSCOHost

Search	Terms	Results
S1	Dialkylcarbamoylchloride OR Dialkyl carbamoyl chloride OR Dialkylcarbamoyl chloride OR DACC	54
S2	leukomed OR cutimed OR sorbact	21
S3	hydrophob* AND dressing*	16
S4	S1 OR S2 OR S3	85
S5	infect* OR wound*	316031
S6	S4 AND S5 (Limits: English Language)	40

Table 8 – Search Strategy: CENTRAL via Cochrane Collaboration

Search	Terms	Results
1	Dialkylcarbamoylchloride	0
2	Dialkyl carbamoyl chloride	1
3	Dialkylcarbamoyl chloride	0
4	DACC	39
5	leukomed OR cutimed OR sorbact	14
6	hydrophob*	374
7	dressing	3069
8	#6 and #7	6
9	#1 or #2 or #3 or #4 or #5 or #8	58
10	wound*	23551
11	infect*	87186
12	#10 or #11	101554
13	#9 and #12	19

2.2.3 Selection of Studies and Data Extraction

Abstracts returned from the above search were assessed for inclusion by two investigators acting independently [JT and Nelson Bua, NB]. If considered suitable for inclusion, the full text of the report was further assessed against inclusion criteria by the same two authors. Any disagreement was resolved by consensus with input from a third [George Smith, GS] and fourth [Amy Harwood, AH] investigator. Study design, patient population, sample size, primary and secondary clinical outcomes and results or clinical impressions of the effects of DACC coated dressings were independently extracted by the primary investigator of this thesis and collated using a structured data extraction table for analysis.

2.2.4 Assessment of Risk of Bias in Individual Studies

The Cochrane risk of bias tool[146] and Jadad[147] scoring system were used to assess methodological quality of randomised controlled trials (RCTs) and cohort studies included in this review. The Cochrane risk of bias tool has become the standard approach for assessing bias in randomised studies,[148] and the Jadad score has been validated for the assessment of risk of bias in studies using established methodological procedures.[149] The Cochrane risk of bias tool classifies articles as being at a low or high risk of bias, whereas the Jadad score is a score between 0 (very poor) and 5 (rigorous).

Two investigators [JT and NB] assessed the risk of bias of included studies independently and collated results in an assessment of risk bias table.

2.3 Results

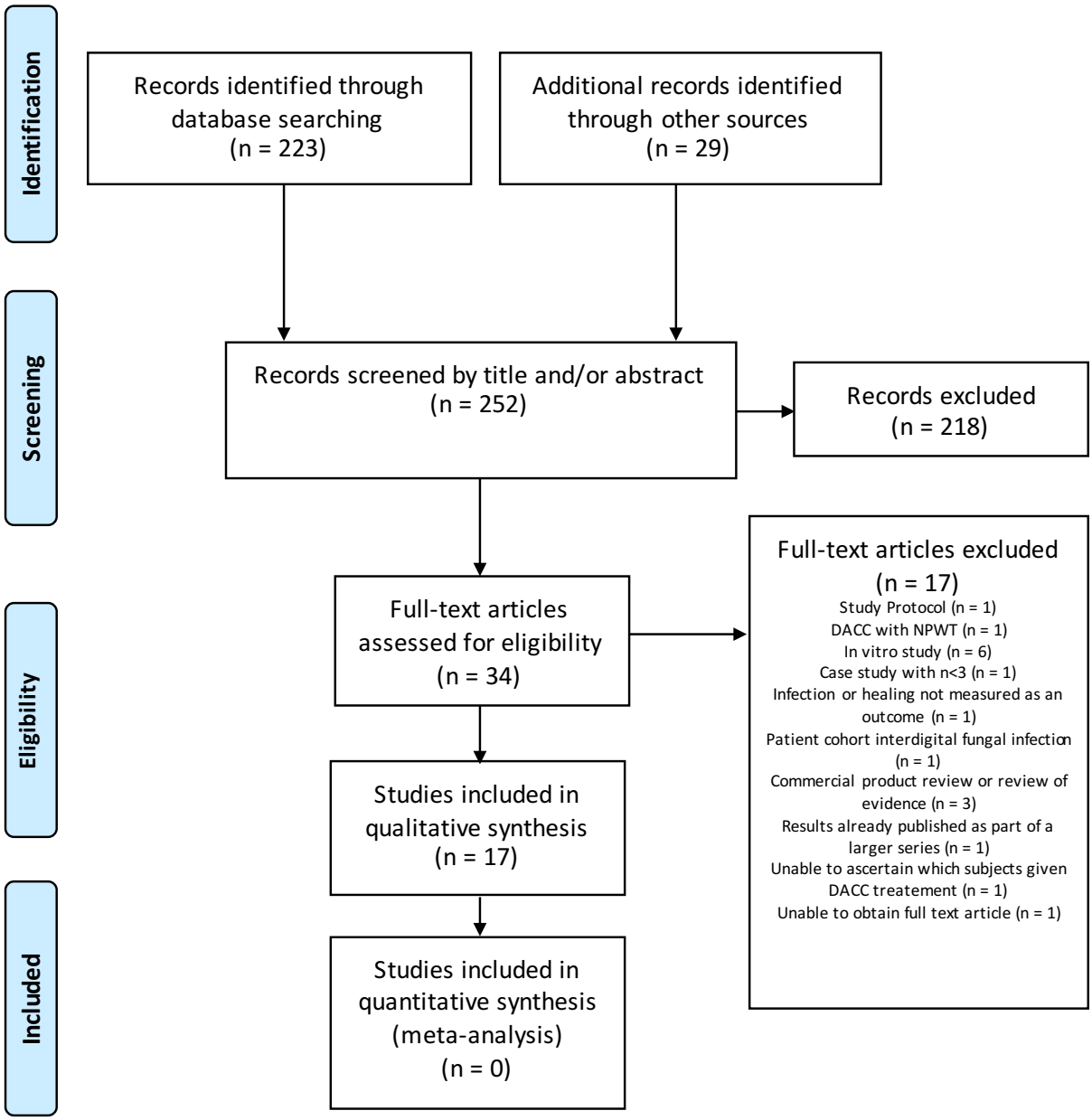
2.3.1 Results of the Search and Included Studies

A PRISMA flow diagram is included (Figure 8) displaying the full results of the above database searches. 252 articles were identified by this search strategy. Of these 252, 34 were considered for inclusion after screening by title and abstract, and the full text sought. After full text review, 17 were considered to be suitable for inclusion.[150-166] A summary of included studies is available as an appendix to this thesis (Appendix 1).

Suitable studies included four RCTs,[159, 160, 165, 166] two cohort studies[154, 158] and eleven case series.[150-153, 155-157, 161-164]

In general, included studies fell into two types; those investigating DACC coated dressings in chronic wounds with or without signs of infection (one RCT,[160] two cohort studies[154, 158] and ten case series,[150, 151, 153, 155-157, 161-164] total 281 patients) and those investigating the use of DACC coated dressings in the prevention of infection in clean surgical wounds (three RCTs[159, 165, 166] and one case series,[152] total 3133 patients).

Figure 8 - PRISMA Flow diagram of included studies



2.3.2 Excluded Studies

The full reasons for exclusion are shown in figure 8.

2.3.3 Risk of Bias in Included Studies

The Cochrane risk of bias tool for RCTs[146] together with Jadad[147] scores demonstrated moderate risk of bias in included studies (tables 9 and 10). The cohort study by Kleintjes[158] was deemed to have a low risk of bias, not accounting for the bias

inherent with the study design. Of the randomised trials, only the trial by Mosti et al[160] had a Jadad score ≥3. Important sources of bias in the three randomised trials examining DACC for prevention of infection[159, 165, 166] included a lack of true randomisation, with alternating sequence allocation used in all three trials, and a lack of allocation concealment and assessor blinding in trials. Of the three, only the 2016 study by Stanirowski[165] attempted any form of blinding or concealment, with surgeons 'blinded' to the allocation of the patient until the point of dressing application (at which point they became aware of allocation due to the physical appearance of the test dressings).

Table 9 - Risk of bias assessment in the included randomised studies

Study	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other Bias	JADAD score
Stanirowski 2014[166]	High	High	High	Low	Low	Low	2
Stanirowski 2016[165]	High	High	High	Low	Low	Low	2
Meberg 1990[159]	High	High	High	Low	Low	Low	2
Mosti 2015[160]	Low	Low	High	Low	Low	Low	3

Table 10 – Risk of bias assessment for the included cohort study

Study	Representativeness of the exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cases and controls on the basis of the design or analysis	Assessment of outcome	Adequacy of follow up of cohorts	Were co-interventions similar between groups
Kleintjes (2015)[158]	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)

2.3.4 DACC-Coated Dressings in Chronic Wound Management

The use of DACC-coated dressings in chronically infected wounds was reported in one pilot RCT by Mosti et al,[160] two cohort studies by Kleintjes et al[158] and Gentili et al,[154] and ten case series.[150, 151, 153, 155-157, 161-164]

Mosti et al[160] performed a pilot RCT comparing the effects of DACC coated dressings and silver impregnated dressings in chronically infected or heavily colonised leg ulcers of vascular origin. The primary outcome measured was a reduction in bacterial load at day 4 of treatment. A reduction of bacterial load of 73.1% was found in the DACC cohort, compared to a reduction of 41.6% in the silver cohort, which was statistically significant ($p<0.01$). Although the difference in reduction of bacterial load between the two dressings was statistically significant, there was no comment regarding the clinical significance of this effect.

Kleintjes et al[158] published a cohort study of 13 patients with partial or full-thickness burn wounds, comparing DACC coated dressings with two branded silver impregnated dressings (Acticoat® and Silverlon®). Included wounds were large enough that 2 or 3 dressing types could be applied to different aspects of each wound. Though no statistically significant differences were seen between dressings, authors report that wounds appeared subjectively cleaner, and wound bacterial burden (based on bacterial cultures) was less in swabs from DACC coated dressing sites with 33% positive cultures, compared to the 37.5% in Acticoat and 44% in Silverlon dressing sites.

Gentili et al[154] published a cohort study of 19 patients (20 wounds) with chronically infected vascular ulcers. All patients were treated for four weeks with DACC-coated dressings changed twice weekly. Pan-bacterial real-time polymerase chain reaction (PCR) was used to assess bacterial load at a wound site before and after a four-week treatment course with DACC-coated dressings. Investigators reported that 66% had a positive outcome in relation to wound size reduction and that these wounds also demonstrated a reduction in bacterial load measured using real-time PCR. This difference was reported to be statistically significant ($p = 0.024$).

Ten case series[150, 151, 153, 155-157, 161-164] with a total of 209 patients reported mainly subjective results following the use of DACC-coated dressings in chronically infected wounds, with a variety of primary and secondary outcomes including, but not limited to, exudate, erythema, odour, slough and pain. All authors felt that there was significant clinical improvement of the affected wounds (reduction in slough and exudate) seen with DACC-coated dressings, but due to the nature of the studies, no quantifiable data could be extracted for synthesis from the studies for the purpose of the review.

2.3.5 DACC-Coated Dressings in the Prevention of Wound Infection in Clean Surgical Wounds

Three RCTs[159, 165, 166] and one case series[152] examined the use of DACC-coated dressings in clean surgical wounds.

Stanirowski et al published both a pilot and a full RCT[165, 166] examining post-surgical wound dressing. Patients undergoing caesarean section were randomised to either DACC coated or standard dressings. The pilot study included 142 patients and the full trial 543 patients. Patients were followed up for 14 days and the presence of SSI was assessed using Centre for Disease Control criteria. In the pilot study the investigators reported a SSI rate of 2.8% in the DACC group compared to 9.8% in the standard dressing group ($p=0.08$). This effect size informed the power calculation for the full RCT, which reported overall SSI rates of 1.8% with DACC compared to 5.2% in standard surgical dressings ($p=0.04$).

Meberg et al[159] included 2441 new born infants, randomised on a 1:1 ratio to either having the umbilical cord stump covered with a DACC coated dressing or daily cleansing with 0.5% chlorhexidine in 70% ethanol solution. Primary outcome was the incidence of new born infection including conjunctivitis, pyoderma, paronychia and omphalitis. Infants were followed up for up to 6 weeks. Overall 377 (15.4%) cases of infection were reported. There was no statistical significance in infection rates between the DACC dressing group and the 0.5% chlorhexidine in 70% ethanol solution group (16.3% and 14.6% respectively, $p>0.05$).

Choi et al[152] presented a case series of seven patients in whom skin grafts were fixed with the use of a DACC-coated wound contact layer and tie-over dressing. All wounds were post-excision of lesion in theatre. No infections were reported.

2.4 Discussion

2.4.1 Summary and Limitations of Evidence for DACC in Chronic Wounds

This purpose of this review, as outlined above, was to examine the evidence for the clinical use of DACC-coated dressings. The evidence examining DACC dressings in chronic wound management is low level (small to medium case studies). In general, the outcomes from these studies is positive however many of the outcome measures were highly subjective. The only randomised controlled evidence in chronic wounds was targeted at the bacterial load within the wound and did not include objective clinical outcomes.[158] This study had a very limited sample size (n=13) and compared dressings in the same wound bed, introducing the possibility of contamination. Reports to date are generally encouraging, but there is clearly a need for rigorously designed trials with adequate sample sizes to produce the level 1 or 2 evidence needed to properly determine the efficacy of this technology in chronic wound management.

2.4.2 Summary and limitations of evidence for DACC as prophylaxis against wound infection

The evidence to support the use of DACC dressings as prophylaxis for SSI in clean surgical wounds is, in theory, of higher quality in that it is based on randomised trials, though the trials reviewed were generally at high risk of bias. Prospective work by Stanirowski et al[166] and earlier work by Meberg[159] did not show a statistically significant difference in infection rates when DACC dressings were used. The design of both studies was sub-optimal including poor treatment allocation and concealment methods, and lack of blinding of participants or investigators.

The full RCT by Stanirowski et al[165] reported a significant reduction in the SSI rates in caesarean section patients receiving DACC compared to standard surgical dressings. However, this RCT had significant weaknesses in trial design. There was no allocation

concealment and nor was the study truly randomised, since consecutive patients were simply alternated between study arms. Primary outcome was reported as SSI according to CDC definitions of superficial or deep SSI. However, the follow up period was only 14 days long, which is insufficient to capture all SSI according to the CDC definition which includes wound infection up to 30 days post procedure.[111] Trial methods were improved for the larger study in comparison to the pilot, in that the wound assessments for the larger trial were performed by investigators blinded to dressing type. This may account for the improvement in the SSI rate in the control group, which was 9.8% in the pilot but reduced to only 5.2% in the full RCT despite identical surgical methods.

Only one article[165] published data on the cost effectiveness of the intervention, which was not taken into consideration in this review. This is due to a significant disparity between the cost of the intervention reported in the article and the actual cost of the intervention on the UK market (mean cost of Leukomed® Sorbact® dressing in the trial reported as €2.80; cost of Leukomed® Sorbact® dressings per dressing on the UK NHS supply chain (as of June 2018) £1.66 to £16.17, based on size – mean £8.82), making any cost analysis difficult to apply to the patient cohort in question in this thesis.

The available evidence does favour DACC coated dressings over conventional basic wound dressings, and in some cases over advanced wound dressings such as silver coated dressings. This provides further evidence that more research into this field of study would be beneficial.

2.4.3 Limitations of the Review

During the search process, at least one article was identified that was classed as a review of the evidence.[167] This was a non-systematic collection of current evidence written on behalf of the product manufacturer that provided a number of references that were included in the search (additional records identified through other sources, figure 7, page 56). Our review, in general, agrees with their findings, however the systematic nature of our review, and the stricter inclusion criteria, meant a much smaller number of studies were included. The product literature did include a large

amount of unpublished data presented at conferences, that was not included in our review, raising the possibility that the conclusions of our review have been impacted by this data not being made available.

This review did include a large number of low-level studies (small case studies). This was due to a relative paucity of good quality scientific studies into the effects of DACC-coated dressings in comparison to currently accepted standard practice.

No meta-analysis of trial data was possible for the included studies, due to differences in trial methodology and outcome measures. There were only two trials[165, 166] with similar enough outcome measures and methods to consider a meta-analysis, however the 2014 Stanirowski[166] trial used the observed effect size to influence the power calculation of the 2016 study.[165] It was felt by study investigators that a meta-analysis of this data would add nothing further to the findings presented in the larger scale RCT.

2.5 Conclusions

DACC coating of dressings shows promise in both the prevention and treatment of wound infections. However currently published studies are not of sufficient quality to make firm conclusions regarding its clinical or cost effectiveness, therefore evidence to support its routine use in clinical practice is lacking. The evidence presented in this review would seem to support further high-quality research into their clinical and cost effectiveness of DACC coated dressings.

CHAPTER 3: STUDY TWO – DIALKYLCARBAMOYLCHLORIDE DRESSINGS IN THE PREVENTION OF SURGICAL SITE INFECTION FOLLOWING NON-IMPLANT VASCULAR SURGERY: A COHORT STUDY

3.1 Objectives

As outlined in Chapter 2, there is a paucity of evidence for the use of DACC-coated dressings in either preventing or treating wound infections. The investigations into the use of DACC-coated dressings in the prevention of SSI in post-surgical wounds healing by primary intention is limited to a single study, conducted in women undergoing caesarean section.[165] The aim of this study, therefore, was to undertake a prospective comparative evaluation of the impact of DACC coated post-operative dressings on the rate of SSI in patients undergoing open non implant vascular surgery, in order to inform the future design of a fully-powered randomised controlled trial.

3.2 Methods

3.2.1 Study Design

This was a prospective, non-randomised comparative study in a single UK centre. It took place in the vascular surgery department at Hull Royal Infirmary, a tertiary referral service for vascular surgery serving a population of around 1.2 million people.[168] A total of 200 participants were recruited, with the initial 100 participants receiving a variety of inert, standard surgical dressings as per the routine clinical practice of the surgeons undertaking the procedure. The second group of 100 participants received DACC coated dressings (Leukomed® Sorbact® – BSN Medical, Hull UK).

3.2.2 Participants

All adult patients undergoing clean or clean-contaminated vascular surgical procedures between August 2015 and February 2016 were considered for inclusion in the study.

3.2.2.1 Exclusion Criteria

The following exclusion criteria were used:

- Planned use of a prosthetic implant
- Known allergy to the components of the DACC-coated dressings
- Patients already undergoing treatment with antibiotics, not including antibiotic prophylaxis as part of the routine surgical care of the patient.

3.2.3 Interventions

Procedures were undertaken by, or under the supervision of, seven vascular surgery consultants. All other aspects of peri-operative care remained unchanged between cohorts. A total of 200 participants were recruited, with the initial 100 participants receiving a non-occlusive, simple absorbent dressing (see section 1.4.2.1.1) as per the routine clinical practice of the surgeons undertaking the procedure. The individual dressing used was the choice of the operating surgeon, but all dressings were basic wound covering-type dressings. The second group of 100 participants received DACC-coated dressings.

All dressings were applied in a sterile fashion in theatres following wound closure. Dressings remained in situ until wound review was undertaken prior to discharge from hospital, or earlier if required, based on clinical need. Standard or DACC-coated dressings were continued for the duration of dressing use at that wound site. All patients were discharged home with extra wound dressings to ensure like-for-like dressing changes in the community.

3.2.4 Assessments

All assessments were undertaken either in the vascular laboratory at Hull Royal Infirmary, or on the inpatient vascular surgery ward, Hull Royal Infirmary.

Participants were assessed at baseline (pre-randomisation), between post-operative-days (POD) 5 and 7, and at POD 30 (±3 days).

3.2.4.1 Baseline Assessments

At baseline, participant demographics, current and past medical conditions, smoking status, current medications and biochemistry results were collected. A general physical examination was undertaken.

3.2.4.2 Assessment of SSI

At follow-up visits, wounds were scored according to the ASEPSIS scale (Table 4, page 49, section 1.3.8.2)[112, 169]. Information was initially collected via a telephone call, where patients were specifically asked about erythema, exudate and wound edge separation, in line with the ASEPSIS score. Patients were then invited to attend for clinical review.

At review, wounds were reviewed by a study nurse or doctor and scored for the presence or absence of erythema, serous exudate, purulent exudate, and wound edge separation. SSI was defined on a per-patient, not per-wound, basis.

On the date of follow-up visit, patient notes were reviewed. This was either the inpatient notes, the hospital discharge letter, letters between secondary care and primary care, the primary care record, or a combination of the above. Notes were reviewed for the specific mention of wound complications, or the prescription of antibiotic therapy.

3.2.5 Follow-up Procedures

Wound assessments were performed on day 5-7 and on day 30. During clinical assessments, any dressings were removed and a short patient interview and review of patient case notes and prescription chart undertaken to allow comprehensive recording of all wound complications and ASEPSIS score, including isolation of bacteria from wounds, return to theatre and prolonged admission.

At clinical review, wounds were assessed for the presence of erythema, exudate and wound separation by a non-blinded clinical reviewer.

3.2.6 Outcomes

The primary outcome for this study was the presence of SSI (ASEPSIS wound score ≥21). Secondary outcomes included evidence of satisfactory healing (ASEPSIS score ≥10).

3.2.7 Statistical Analysis

Data was collated into *IBM SPSS* (IBM SPSS corporation version 22, Rochester, United States) to facilitate statistical analysis. Data is presented descriptively using mean (SD) or *n* (%) for each group. The groups were compared using chi-square tests or fisher's exact tests for categorical data and t-tests for continuous data. Infection was dichotomised into presence or absence (of infection) and statistical differences between groups were compared using chi-square tests. In order to measure the association level, crude odds ratio (OR) and the 95% corresponding test-based confidence interval (CI) were calculated. A logistic regression analysis was undertaken to control for the effects of other variables which might be expected to influence healing. A *p*-value of <0.05 was considered statistically significant.

3.3 Results

3.3.1 Baseline Characteristics

200 patients were recruited from 1st August 2015 to 29th February 2016, 120 men and 80 women, with a mean age of 63 (range 27-97) years. Each group had 100 patients. Comparative data for the two groups is summarised in table 11.

Table 11 – Demographic data of participants.

	DACC dressings group (*n* = 100)	**Standard dressing group (*n* = 100)**	**P=**
Age (range)	63 (29 – 94)	63 (27-97)	0.54
Male Gender	54	66	0.11
Diabetic Insulin use	39 24/39	52 21/52	0.08 0.07
Cardiac Disease	42	39	0.66
Respiratory disease	25	47	0.01**
BMI (range)	28 (17- 45)	27 (19-43)	0.81
Smoking Status Ever smoked Current smoker	 92 58/92	 92 50/92	 1.0 0.38
Closure method Continuous Interrupted	 97 3	 92 8	 0.21 0.21
Grade of Surgeon Consultant Senior trainee (ST5-8) Junior trainee (CT1-ST4)	 52 43 5	 54 38 8	 0.88 0.56 0.56
Surgical procedure performed Limb revascularisation Major limb amputation Minor amputation Carotid Endarterectomy Open varicose vein surgery	 27 38 0 4 18	 13 35 19 8 20	 <0.05** 0.76 <0.001** 0.37 0.85

Dialysis fistula formation	8	3	0.21
Other	5	2	0.44
ASA grade			
ASA 1	8	7	0.78
ASA 2	24	29	0.52
ASA 3	54	51	0.77
ASA 4	14	11	0.66

***denotes statistical significance between groups*

3.3.2 Clinical Outcomes

Fewer patients had SSI in the DACC-coated group than the standard group at 5-7 days (1/100 and 10/100 respectively, OR = 0.09 (95% CI: 0.01, 0.072, p= 0.005)). In those remaining at risk, there was no difference in SSI at the 30-day wound assessment (9/99 and 9/90, p=0.832). There was no difference in adequate wound healing at any time. Wound classifications recorded for all wounds are summarised in table 12.

Table 12 – Incidence of SSI in DACC vs standard dressings

		DACC dressings group *n* = 100 (*n* at risk)	**Standard dressings group *n* = 100 (*n* at risk)**	**P-value**
Day 5-7	SSI	1 (100)	10 (100)	0.01**
	Adequate Healing	85 (100)	74 (100)	0.07
Day 30	SSI	9 (99)	9 (90)	0.83
	Adequate Healing	88 (99)	75 (90)	0.37
Total	Incidence SSI	10%	19%	0.11

***denotes statistical significance between groups. SSI – Surgical site infection (ASEPSIS score ≥21). Adequate healing – ASEPSIS score ≤10)*

For SSI at day 5-7, the single incident of SSI in the DACC dressing group required 7 days of intravenous (IV) antibiotics. In the non-DACC group, all 10 patients with SSI at day 5-7 were treated with antibiotics; two of these required IV antibiotics, one for 21 days in total. The other 8 patients were treated with oral antibiotics, with 5/8 treated for 14 days total. At 30 days, there was no significant difference in readmission rates due to SSI between the two groups (7/99 and 9/90, p=0.470).

Logistic regression was performed to control for the effects of recorded variables which would be expected to impact upon the risk of SSI as listed in table 13. Seven potential confounding variables were included in the model.[170] After regression analysis, the type of dressing used remained the most prominent predictor in early SSI (p=0.028) with an odds ratio of 0.09 (95% CI: 0.01, 0.77).

Table 13 - Potential confounders to SSI included in Logistic regression.

Variable	Wald	df	Sig.	OR	95% CI	
					Lower	Upper
Presence of Diabetes	3.706	1	0.054	0.529	0.277	1.012
BMI	0.294	1	0.588	0.984	0.926	1.044
Current Smoking	1.345	1	0.246	0.699	0.382	1.280
Grade of operating surgeon (Consultant vs Trainee)	0.141	1	0.707	0.891	0.488	1.627
Early SSI	4.840	1	0.028**	0.094	0.011	0.772
ASA grade ≥3	2.464	1	0.116	1.771	0.868	3.617
Type of surgery	0.035	1	0.851	1.070	0.529	2.163

*Type of surgery is divided into treatment for critical limb ischaemia vs other vascular surgery (** = p<0.05, df = degrees of freedom, Sig.= significance, OR = odds ratio, CI = confidence interval, BMI = Body mass index, SSI = Surgical site infection, ASA = American Society of Anaesthesiologists)*

3.4 Discussion

This small comparative trial suggests that dressings coated with DACC may reduce the rate of SSI in non-implant vascular surgery patients. The incidence of SSI is likely

to increase with the growing prevalence of diabetes and obesity, combined with higher rates of complex surgical intervention being performed in a population advancing in age.[88, 171] For this reason, strategies to reduce rates of SSI should be thoroughly investigated, a belief supported by the WHO.[101, 103] Prior in-vitro evidence strongly supports the proposed mechanism of action by which DACC might be expected to limit ingress of bacteria into incision wounds.[143, 172, 173] DACC coated dressings act by trapping and physically removing bacteria (rather than being bactericidal) which, in the context of wider societal concerns regarding antibiotic resistance make this action particularly attractive as a novel intervention as the development of bacterial resistance is less likely. DACC dressings have also been shown to bind to organisms that are antibiotic resistant in vitro.[143, 144] Results of in-vivo application of DACC coated dressings in chronically infected wounds have also been promising both in terms of bio-burden reduction and enhanced clinical evidence of healing.[151, 154, 158, 160] Equally, no absorption of DACC into the wound surface is known to occur and no evidence of any adverse effects have been reported, allowing its potential application to all patient groups.

This study was intended as a proof of concept study to examine the possible effectiveness of DACC impregnated dressings as a prophylactic measure in reducing rates of SSI in a cohort of patients at an inherently high risk of infection. It has shown an apparent reduction in incidence of SSI in a cohort of clean and clean contaminated non-implant vascular surgery when applied post-operatively. These results are in keeping with evidence supporting the use of DACC coated dressings as prophylaxis against SSI in fit and well patients undergoing caesarean section.[165] The maximal protective effect appears to be in the early post perioperative period, prior to the 5-7 day assessments. The timing of the apparent action reported in these results appears logical since the mechanism of action of DACC would be prevention of ingress of bacteria into freshly incised wounds which have yet to reepithelialise. Logistic regression suggested a significant impact of the dressings for all instances of SSI when controlling for potential confounding variables expected to impact healing, such as smoking and diabetes.

3.4.1 Limitations of the Study

There were several potential sources of bias within this study. The nature of the study design was as an exploratory proof of concept study prior to an intended randomised trial. Although patients were not randomised, groups were well matched for most variables. There is the possibility that introducing a study, or a study dressing, reduces the rate of measured SSI through observer bias or through bias of the study participant (the so-called Hawthorne effect[174, 175]). However, although the subjective aspects of the ASEPSIS scoring system were undertaken by a study clinician, treatment for infection, antibiotic use, and infection recorded in the patient case notes were contemporaneous and recorded by the patients' main care team. Patient reported outcomes were not included in the final analysis. Study follow up, at 5-7 days and 30 days, was standardised across both cohorts, so any Hawthorne effect should be seen in both groups.

A further source of bias was the lack of blinding. Leukomed® Sorbact®, the DACC-coated dressing in the study, contains a green colouring to the wound contact layer in order to identify it as a DACC-coated dressing. Because of this, blinding is difficult, though not impossible to achieve in any trial studying its effects, leading to the open label nature of this study. Future randomised studies into DACC-coated dressings should make use of a wound assessor that is blind to the dressing type used, after removing and disposing of dressings in opaque bags.

3.5 Conclusions

SSI is a significant problem which is likely to rise as increasing numbers of surgical procedures are performed in an ageing and co-morbid population. Results from this study support the hypothesis that DACC coated post-operative dressings may reduce rates of SSI when applied to wounds healing by primary intention. An adequately powered randomised controlled trial comparing DACC coated and conventional dressings is warranted to provide the robust evidence essential prior to this technology being adopted into routine practice.

CHAPTER 4: STUDY THREE – A PILOT FEASIBILITY RANDOMISED CONTROLLED TRIAL INVESTIGATING THE EFFECTIVENESS OF DIALKYLCARBAMOYLCHLORIDE COATED POST-OPERATIVE DRESSINGS VERSUS STANDARD CARE IN THE PREVENTION OF SURGICAL SITE INFECTION IN CLEAN OR CLEAN CONTAMINATED VASCULAR SURGERY

4.1 Objectives

Study one and study two identified that there is evidence to support the use of DACC coated dressings post-operatively for the prevention of SSI. However this evidence is of insufficient quality to prompt a widespread change in current clinical practice. The systematic review performed (study one*)* identified only a single RCT examining DACC coated dressings being used to prevent SSI, and a cohort study (study two) identified that there is potential for DACC coated dressings to have a significant impact on SSI rates in patients undergoing vascular surgery but remains at high risk of bias due to a lack of randomisation and a lack of blinding.

Randomised controlled trials are considered the most rigorous way of examining the effect of a given intervention. However, they are also costly and often difficult to conduct.[176] Delivering such a trial to investigate the effect of DACC coated dressings may be complex, and risks not meeting recruitment or retention targets, due to a variety of reasons.[177] Pilot studies do not guarantee success in the main study, but do increase the likelihood of success, by fulfilling a range of important functions and providing valuable insights to the study team.[178] There are multiple benefits to performing a pilot study in advance of a large, multi-centre, RCT, and their use is becoming more commonplace.[179, 180]

The aim of this study, therefore, was to conduct a pilot feasibility RCT, in order to test the design of a fully powered RCT to identify whether dressing post-operative

wounds with DACC-coated dressings is more clinically and cost effective than conventional dressings in preventing SSI in patients undergoing clean or clean-contaminated vascular surgery.

4.2 Methods

4.2.1 Study Design

A single centre pilot RCT was undertaken in a tertiary vascular surgery unit in the United Kingdom (Academic Department of Vascular Surgery, Hull and East Yorkshire Hospitals NHS Trust). Ethical approval was granted by a research ethics committee (16/LO/2135) and the study was conducted in accordance with the Declaration of Helsinki (1975).[181] The study was prospectively registered with clinicaltrials.gov (NCT02992951). All patients gave informed, written consent prior to any involvement with study activities.

4.2.2 Inclusion Criteria

- Adults ≥18 years undergoing clean or clean-contaminated vascular or surgery, with wounds closed by primary intention.
- Able to understand the PIS and supplementary materials, and capable and willing to give informed consent and follow the protocol requirements (including attending all follow-up visits and completing written questionnaires).

4.2.3 Exclusion Criteria

- Patients on antibiotics for other conditions not related to the index procedure at the time of surgery
- Patients undergoing carotid endarterectomy
- Allergies to any component of either the DACC-coated dressing or the control dressing
- Inability to give informed consent due to incapacity (as defined by the Mental Capacity Act 2005)
- Use of investigational drug/device therapy within preceding 4 weeks that may interfere with this study.

4.2.4 Recruitment Process

Suitable patients were identified for this study by the principle investigator of this thesis (Dr Joshua Totty) or a clinical member of the Academic Vascular team, from operating theatre lists, waiting lists, outpatient clinics, or on ward rounds. Patients were approached in one of two ways: where time permitted (such as an elective surgical procedure planned a number of weeks in advance) patients were contacted via telephone and an information sheet sent in the post. Where procedures were semi-elective or planned at short notice patients were approached on admission to the inpatient ward and given an information sheet in person.

Patients were then contacted again either on their admission (if they were initially contacted at home) or after being given sufficient time to read and understand the information, and discuss it with friends or family. Study doctors then obtained informed written consent (Appendix 3 to this thesis) from those patients that expressed an interest in the study and met the inclusion/exclusion criteria.

4.2.5 Randomisation

Participants were randomised to treatment groups in a 1:1 ratio by either a member of the study team or a member of the theatre team, using computer-generated numbers in random permuted blocks via an online randomisation service (Sealed Envelope Ltd, London, UK), stratified for implant/non-implant, wound site (upper limb/lower limb/trunk) and diabetes (yes/no).

Due to the visual differences between the intervention and control dressing, operating clinicians were unable to remain blinded to randomisation. This was therefore an observer blinded clinical trial.

4.2.6 Study Intervention and Procedures

4.2.6.1 Pre-operative Procedures

Patients received standardised care pre-operatively. Hair removal (clipping), and anaesthesia were conducted according to local hospital policy. Skin preparation was standardised to povidone-iodine in aqueous solution.

4.2.6.2 Intra-operative Procedures

Patients were randomised to undergo post-operative wound dressing with either a DACC-coated occlusive absorbent dressing (Leukomed® Sorbact®, BSN Medical, Hull, UK) or a non-DACC-coated occlusive absorbent control dressing (OPSITE® Post-op, Smith & Nephew, Hull, UK).

No topical antimicrobials were used intra- or post-operatively. All initial dressings were applied to the wound in the operating theatre under sterile conditions. Where patients had more than one wound (such as graft harvest and implant sites), all eligible wounds were dressed according to the dressing allocation.

4.2.6.3 Post-operative Procedures

Dressings were replaced on day 2 post-procedure, and again at the time of first wound review (5-7 days). Interim dressing changes were undertaken where there was a clinical indication such as soiling or loss of adhesion. On discharge from hospital, patients were provided with further dressings of the same variety to ensure like-for-like dressing changes up to the point of wound healing.

Where study dressings were clinically unsuitable for a wound (such as excessive exudate or bleeding), non-trial dressings were applied, and their use recorded as a protocol deviation.

Patients did not routinely have microbiological swabs taken from the wound. Wound swabs were taken:

- If the wound had a purulent exudate
- If the wound was erythematous AND the patient had a fever >38°C
- Before the commencement of antibiotics for a clinical diagnosis of wound infection
- If the patient required blood cultures per local policies AND had any signs or symptoms of wound infection
- If the patient required further surgical procedures e.g. wound debridement or abscess drainage

4.2.7 Assessments

All assessments were undertaken either in the vascular laboratory or on the inpatient vascular surgery ward in Hull Royal Infirmary. Participants were assessed at baseline (pre-randomisation), between post-operative-days (POD) 5 and 7, and at POD 30 (±3 days). A further assessment took place between 6 and 12 months post procedure to investigate ongoing problems and further resource use.

4.2.7.1 Baseline Assessments

At baseline, participant demographics, current and past medical conditions, smoking status, current medications and biochemistry results were collected. A general physical examination was undertaken. Patients also completed questionnaires to assess QoL.

4.2.7.2 Assessments During Follow-up Visits

Follow-up visits took place between POD 5 and 7, and at POD 30, ± 3 days. At each visit, a short patient history was used to identify any problems that the patient may have had with their wound between reviews. Patients were asked specifically about wound problems, visits to the GP or practice nurse, and courses of antibiotic therapy. Prior to interview, patients completed questionnaires to assess QoL.

4.2.7.2.1 Assessment of SSI

At follow-up visits, wounds were scored according to the ASEPSIS scale (Table 4, page 49, section 1.3.8.2)[112, 169]. Wounds were reviewed by a study nurse or doctor blinded to the allocated dressing type and scored for the presence or absence of erythema, serous exudate, purulent exudate, and wound edge separation.

On the date of follow-up visit, patient notes were reviewed. This was either the inpatient notes, the hospital discharge letter, letters between secondary care and primary care, the primary care record, or a combination of the above. Notes were reviewed for the specific mention of wound complications, or the prescription of antibiotic therapy.

At the review on POD 30, patients completed the PHE post-discharge questionnaire (Appendix 5 to this thesis) (see section 1.3.8.3), designed to identify wound problems in the period between clinical reviews.

4.2.7.2.2 Assessment of Quality of Life

At review, patients completed both the SF-36 and the EQ-5D questionnaires for the assessment of generic QoL.

4.2.7.3 Further Assessments

4.2.7.3.1 Assessment of Quality of Life

Patients were sent QoL questionnaires through the post 3 months post-operatively (±2 weeks).

4.2.7.3.2 Assessment of SSI

At 6-12 months post procedure, patients were contacted by telephone, in conjunction with a thorough review of hospital clinical notes and GP summary care records (where available). Any further wound problems past POD 30 alluded to by the patient or the clinical notes triggered a further face-to-face clinical review.

4.2.8 Follow-up Procedures

If participants were still an inpatient at POD 5-7, the first study visit was conducted on the ward by a member of the study team. If the patient was discharged prior to POD 5, they were given an appointment to attend the vascular laboratory, Hull Royal Infirmary, as an outpatient. If patients failed to attend face-to-face assessments, further appointments were offered. Where patients did not attend follow-up appointments, retrospective data was collected by means of a telephone call to categorise reasons for missing appointments.

To maintain blinding, at the time of wound review, dressings were removed and disposed of in opaque refuse bags before a clinician (who was not present for dressing take down) completed an ASEPSIS score. Clinicians who completed the ASEPSIS score then left the room/patient bed area before dressings were applied, to maintain blinding.

4.2.9 Outcome Measures

This study was intended as a pilot study, in order to influence the design of a fully powered RCT. As such, outcomes were divided into two distinct categories – *feasibility* outcomes and *clinical* outcomes.

4.2.9.1 Feasibility Outcomes

The following outcomes were assessed with regards to the feasibility of undertaking a large scale RCT investigating the effectiveness of DACC-coated dressings in the reduction of SSI:

- The measured effect size of the trial intervention in order to inform the power and design of a full RCT
- The suitability of the trial intervention in different wound types/locations
- The suitability of the inclusion/exclusion criteria
- The suitability of outcome assessment measure(s)
- Eligibility rates and reasons for non-eligibility
- Participant recruitment rates and reasons for non-recruitment
- Follow-up and study retention rates and reasons for drop-out/non-attendance
- Fitness for purpose of follow-up arrangements
- Fitness for purpose of data collection methods
- Rates of participant withdrawal from the trial; participant response rates to questionnaires; likely rates of missing study data.

4.2.9.2 Clinical Outcomes

4.2.9.2.1 Primary Clinical Outcome

The primary clinical outcome was the incidence of SSI within 30 days of surgery, measured by an ASEPSIS score ≥ 21 (Section 1.3.8.2),[112, 169] or according to the CDC definition of SSI.[73, 74]

4.2.9.2.2 Secondary Clinical Outcomes

A number of secondary clinical outcomes were assessed as part of this study. These were:

- The incidence of SSI at 90 days for implant patients only
- Satisfactory healing - total ASEPSIS score ≤10 at 30 days post-surgery for non-implant surgery and implant patients
- Satisfactory healing - total ASEPSIS score ≤10 at 90 days post-surgery for implant patients only
- Quality of Life
- Time to return to normal activity/work
- Resource use and cost analysis: Patient and physician reported need for primary care review, requirement for antibiotics, extra hospital visits, readmission and re-intervention rates
- 30-day mortality

4.2.10 Sample Size Calculation

The overall effect size seen in study two was used to calculate the sample size for an RCT with SSI as the primary outcome. To demonstrate the same reduction in the incidence of SSI, namely from 19% to 10% or less, at 90% power and 5% significance, 320 patients will be required in each trial arm. To allow for a 10% patient drop out then a total of 712 patients will be required, with 356 patients in each arm of the trial.

The pilot study aimed to recruit one fifth (20%) of the patients required for a full-scale RCT (*n* = 144).

4.2.11 Statistical Analysis

Data were collected into IBM SPSS (IBM SPSS Corporation, version 23; Rochester, USA) to facilitate statistical analysis, with a two-sided p-value of <0.05 taken as the level of significance where appropriate.

For feasibility outcomes, simple categorical data were presented descriptively using mean (SD), median (IQR) for skewed data, or *n* (%) for each group.

For clinical outcomes, data was analysed on an intention-to-treat (ITT) basis. Data were presented descriptively using mean (SD) or *n* (%) for each group. The groups were compared using Pearson's χ^2 test or Fisher's exact tests for categorical data and

t-tests for continuous data. The primary outcome, SSI, was dichotomized into presence or absence of infection, and statistical differences between groups were compared using chi-squared tests.

For the primary outcome, logistic regression analysis was undertaken with SSI as the dependant variable and randomisation group as an independent variable. The model was adjusted for confounding variables and surgical site. The regression model performance was assessed by the Hosmer and Lemeshow Test, which if not significant indicates a good model fit.[182] Logistic regression was also undertaken for satisfactory healing. For QoL, an intragroup and intergroup analysis was performed, using Friedman's two-way analysis of variance (ANOVA) test to assess for intragroup differences, and Mann-Whitney U tests to assess for intergroup differences of the SF-36 responses. For the EQ-5D, responses were dichotomised into "no problems" and "problems," and intragroup analysis conducted using related sample's Cochrane's Q test, with Pearson's χ^2 tests for intergroup analysis. For time to event data (time to return to work and mortality), Kaplan Meier and log rank tests were used to calculate and compare event rates between groups.

4.2.11.1 Missing Data

Where patients did not attend for follow-up visits, data was sourced through other means (clinical notes, telephone calls and GP summary care records). Where no data was available, patients were treated as having not experienced SSI for the purposes of analysis.

4.2.12 Data Recording

Data was recorded as a hard copy in a specially designed, individual Case Report Form (CRF). Each participant had their own, corresponding CRF. From these documents, electronic records were kept by recording the data into an anonymised spreadsheet (Microsoft Excel 2010, Microsoft Corporation, Redmond, Washington, USA).

4.2.13 Ethical Considerations

The study conduct, analyses, dissemination of findings and writing of this thesis has been performed in accordance with the principles of the declaration of Helsinki. The best interests of participants, their safety and their satisfaction were the primary

concern of every individual involved in this project. All investigators underwent formal good clinical practice training prior to commencing their involvement with the studies contained within this thesis, and had a valid certification at all times.

The study protocol, PIS, questionnaires, informed consent form and specimen GP letter were submitted to the London – Harrow Research Ethics Committee for review and ethical approval. Appropriate ethical approvals were obtained and then submitted to the research and development department for Hull and East Yorkshire Hospital Trust. The trial was registered and made available as recommended. Progress reports and notification of any adverse event were provided to the Ethics Committee according to the regional regulations and guidelines. The study was also monitored in accordance with the Hull and East Yorkshire NHS Trust's research and development department standard operating protocols.

Participants were only included in the study if they fit the inclusion / exclusion criteria defined earlier in this chapter. Informed consent was obtained from all participants prior to entering the study. Patient participation in the trial was entirely voluntary. Participants had the option to withdraw from the trial at any stage without providing any explanation. Furthermore, they were reassured that their standard clinical care would not be affected by withdrawing from the study. Participants were also encouraged to express any concerns or questions to the investigators.

Patient confidentiality was maintained throughout. All information collected about the trial participants were collated using unique patient identifying numbers. Participants names and details were anonymised and were never available in accessible data sets, or any other reports. All data was kept electronically in password-protected datasets in a private folder, which was accessible only by members of the study team from computers in the locked Academic Vascular Surgical Unit at Hull Royal Infirmary.

Hard copies of the participants' data were kept at the Academic Vascular Research Unit with appropriate archiving arranged for the next five years. Excel, SPSS and Stata databases used for the data maintenance and analysis were kept in encrypted files with password control on the Hull and East Yorkshire Hospitals NHS trust secure

servers and trust approved onsite computers. The study was primarily funded through the internal funding by the Academic Vascular Surgery Unit and the Hull and East Yorkshire Hospitals NHS Trust.

4.3 Results – Feasibility Outcomes

4.3.1 Eligibility and Reasons for Non-Eligibility

Between January 19th 2017 and February 6th 2018, 331 patients were screened for eligibility for inclusion into the study. Screening was conducted as per the methods outlined in section 4.2.4. Of these 331, 240 patients were eligible for inclusion (72.51%). Reasons for non-eligibility are shown in table 14.

Table 14 – reasons for non-eligibility

Reason for non-eligibility	n (%)
Undergoing carotid endarterectomy	35 (38.89%)
Concurrent antibiotic therapy	33 (36.67%)
Lacks capacity due to dementia or other conditions	7 (7.78%)
Other reasons not stated above	15 (16.67%)

4.3.2 Recruitment and Reasons for Non-Recruitment

Of the 240 eligible patients screened, 148 patients were recruited and gave written consent for inclusion in the study (61.67%). 144 patients were subsequently randomised. 43.50% of screened participants were therefore successfully randomised for the study.

A variety of reasons for eligible patients not being recruited were encountered by the study team. These are shown in table 15.

Table 15 – Reasons for non-recruitment

Reasons for non-recruitment	**n (%)**
Unwilling or unable to return for follow-up visits	40 (43.01%)
Did not wish to participate in a research trial	14 (15.05%)
Participating in a competing trial	13 (13.98%)
No reason given by participant	9 (9.68%)
Other reasons not stated above	17 (18.28%)

Four patients that were recruited to the study were subsequently not randomised; one patient decided not to undergo surgery, one patient withdrew their consent to participate in the trial prior to randomisation, one patient was not randomised due to an error in theatres, and one patients' procedure was cancelled and rearranged for a time after the study had ended.

Patients were recruited at a median rate of 10 patients per month (IQR 8.25 – 12.75). Figure 9 shows cumulative recruitment across the 13 months the study was operational.

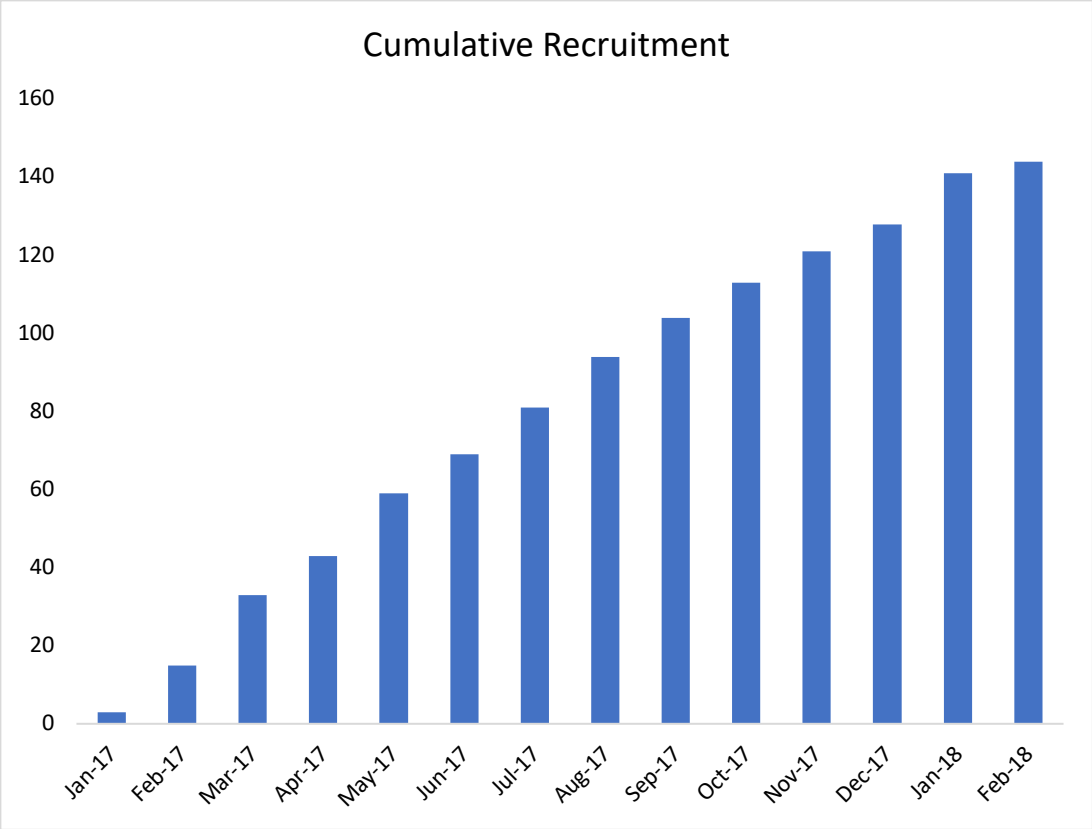


Figure 9 - Cumulative Recruitment

4.3.3 Study Retention, Dropout Rate, and Reasons for Withdrawal

Of the 144 patients randomised, 16 patients actively withdrew from the trial during the study period. Reasons for withdrawal are shown in table 16. The mean time to withdrawal was 14.93 (±23.60) days, median time 6 days (IQR 1-28).

Table 16 – Stated reasons for withdrawal from the trial

Reason for withdrawal	**n**
Unwilling or unable to attend follow up visits	8
Felt being in the trial had caused a surgical site infection	2
Withdrawn by study team as wound not primarily closed	1
Withdrawn by study team as wound not requiring dressing	1
Unable to attend due to work commitments	1
Withdrawn with no reason given	3

7 patients died during the follow-up period, unrelated to study outcomes or interventions (two myocardial infarction, one ischaemic heart disease, one pneumonia, one end stage renal failure, one sepsis secondary to an infected diabetic foot ulcer, and one patient who passed away in the community whose cause of death was unable to be determined). 2 of these patients passed away within 30 days of their procedure (pneumonia and myocardial infarction). 11 patients attended no follow-up visits and returned no questionnaires, and were therefore classed as lost to follow-up. 110 randomised patients therefore completed the study, with varying compliance with the study protocol. This amounts to a combined dropout rate of 23.6%. Figure 10 shows a consort diagram of the flow of patients through the trial.

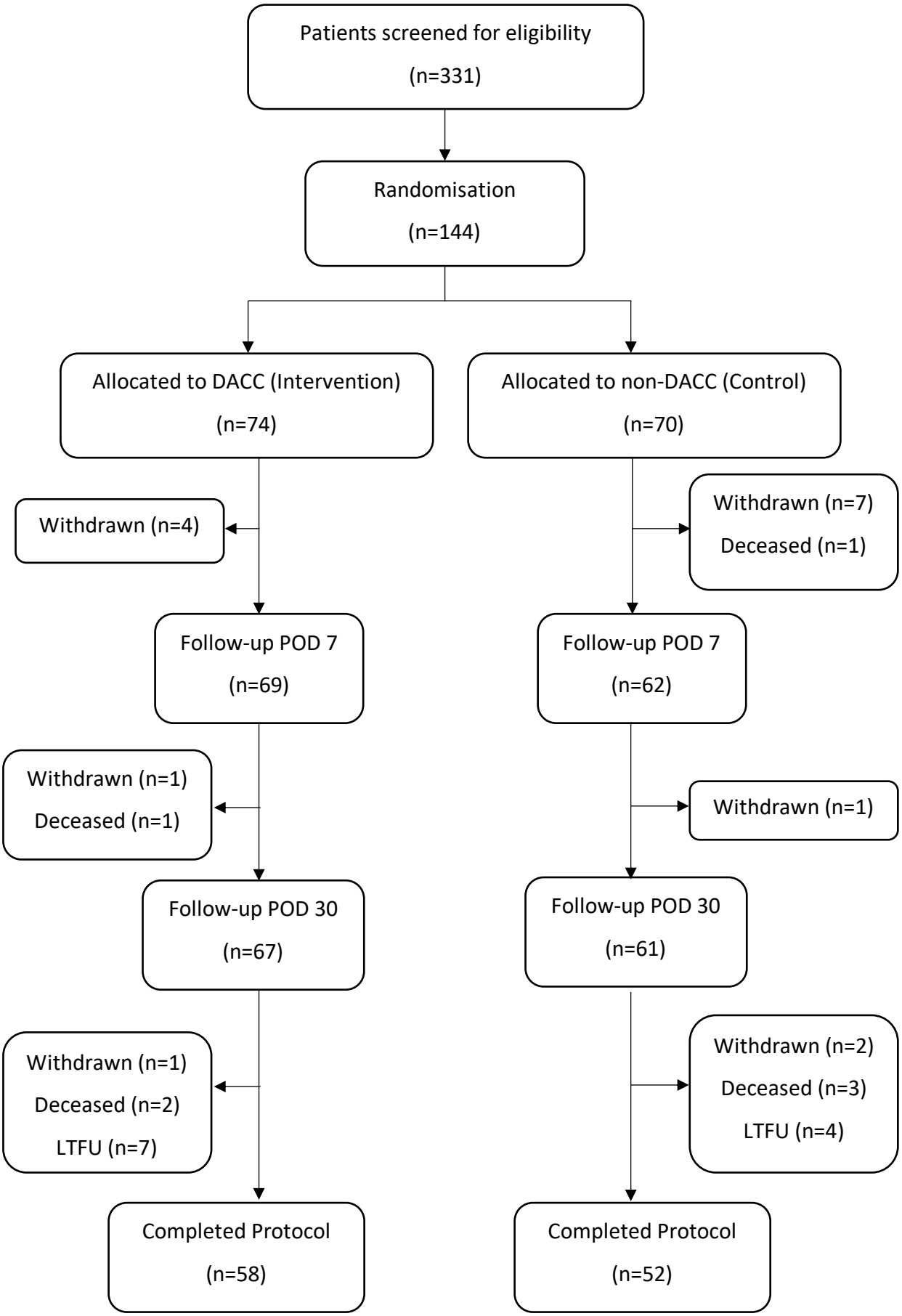


Figure 10 – CONSORT diagram showing progression of participants through the pilot trial.

POD = Post-operative day

4.3.4 Follow-up Rates and Reasons for Non-Attendance

With regards to follow up visits, of 131 possible POD 5-7 visits (not including patients who had died or withdrawn from the trial), 95 were completed (72.52%). Of 128 possible POD 30±3 visits, 81 were completed (63.28%). Table 17 shows rates of appointment attendance divided by surgery subtype. Data on SSI within 30 days was available for 119 participants (82.6%). 3 patients withdrew from the trial after experiencing SSI; their data was included in the final primary outcome analysis.

Table 17 – Rates of follow-up appointment attendance divided by surgery type

Surgery	**POD 7 attendance, n=131 (%)**	**POD 30 attendance, n=128 (%)**
Open abdominal	84.6%	73.1%
Lower limb arterial	72.5%	60%
Open varicose vein	83.3%	75%
Major limb amputation	81.3%	60%
Renal dialysis access	50%	38.5%
Other	74%	63.3%
Total	*72.5%*	*63.28%*

4.3.5 Participant Response Rate to Questionnaires

Figure 11 shows the combined response rates to questionnaires at the time points within the study. Questionnaires were marked as 'incomplete' if one or more questions within them were not complete – for this reason a number of questionnaires that were partially completed were not included in the final calculations of return rate.

Return rates declined across the study period, with mean return rates of 66.2%, 53.4%, 50.0% and 50.3% at each time point.

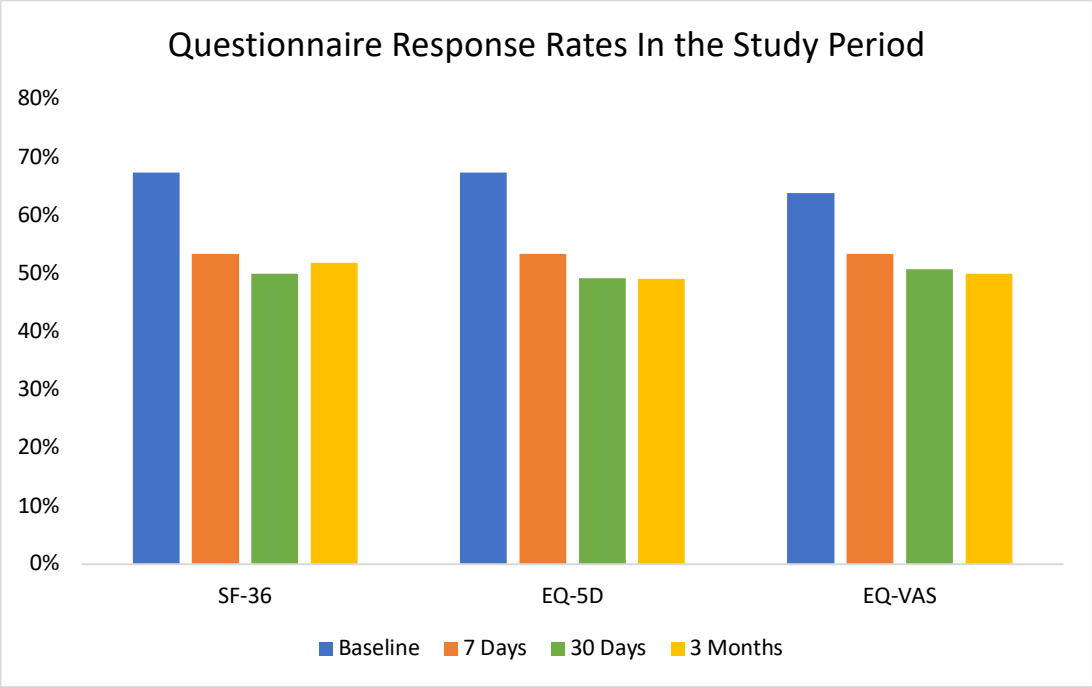


Figure 11 - Participant response rates to questionnaires

Rates are expressed as a percentage (%) of the total available responses at each time point. For a questionnaire to be marked as complete, all questions must have been completed by the participant.

4.3.6 Suitability of the Trial Interventions

16 patients had recorded protocol deviations related to trial interventions. Nine patients were found on trial visits to have non-protocol dressings in situ, with no reason given for the change. Two patients had non-protocol dressings as their wounds had high levels of exudate requiring absorbent dressings to be placed. One patient in the DACC arm experienced a desquamating allergic reaction to an intravenous antibiotic given per-protocol as pre-operative prophylaxis, necessitating a non-adhesive dressing pad to be used on POD 2. Two patients in the control arm had inadine (active) placed on the wound; 1 patient in the control arm had wound dressing with absorbent pads, followed by silver dressings, and 1 patient in the DACC arm had NPWT; all after experiencing SSI. In general, both the DACC coated dressing and the control dressing were well tolerated by study participants.

There were no incidents of allergic reaction to the DACC coated dressing. There was one incident of traction-blistering of the skin surrounding an abdominal wound

caused by the adhesive of the DACC-coated dressings. Importantly, there was no evidence of reaction to the DACC-coated component of the dressing.

4.4 Results – Clinical Outcomes

4.4.1 Baseline Characteristics

144 patients were recruited and randomised into the study between January 19th, 2017, and February 6th, 2018, of which 94 were male (65.3%). 74 patients were randomised to receive DACC-coated post-operative dressings, with 70 randomised to receive standard dressings. The average age of participants was 63.15 (±12.33) years. Groups were well matched at baseline. Tables 18 to 21 outline baseline characteristics, medications, procedures performed and intraoperative procedures for each group.

Overall, 29.9% of participants had diabetes mellitus, 77.1% of participants were current or ex-smokers, 50.3% of patients had PAD, and 41% had comorbid cardiac disease.

Table 18 – Baseline demographic data

	Non-DACC Coated (n=70)	DACC Coated (n=74)
Male	46	48
Female	24	26
Age	62.36 (±12.31)	63.91 (±12.38)
BMI	27.73 (±5.89)	27.65 (5.84)
Smoking Status		
Never	15	18
Ex	40	35
Current	15	21
Diabetes Mellitus		
None	47	54
Diet Controlled	3	1
Tablet Controlled	9	9
Insulin Dependent	11	10
CVA	8	8
Hypertension		
Uncontrolled	3	2
One Agent	25	14
Two Agents	10	22
Three or More Agents	11	11
Cardiac Disease	28	30
PVD	35	37
Respiratory Disease	14	16
Renal Impairment	16	19
Baseline Creatinine	160 (±182)	152 (±198)
GI Disease	8	6
Baseline Albumin	36 (±5)	35 (±6)

CVA = Cerebrovascular accident. PVD = Peripheral vascular disease. GI = Gastrointestinal disease. BMI = Body mass Index

Table 19 – Number of patients taking significant medications

Medication Class	Non-DACC Coated (n=70)	DACC Coated (n=74)
Anticoagulant	9	9
Oral Corticosteroid	2	3
Inhaled Corticosteroid	6	12
NSAIDs	3	4
Platelet Inhibitor	35	40

NSAIDs = Non-steroidal anti-inflammatory medications.

Table 20 – Comparison of procedures performed

	Non-DACC Coated (n=70)	DACC Coated (n=74)
Open abdominal	14	12
Lower limb arterial	29	28
Open varicose vein	6	8
Major limb amputation	7	9
Renal dialysis access	5	8
Other	9	9

Table 21 – Comparison of intraoperative factors

	Non-DACC Coated (n=70)	DACC Coated (n=74)
ASA Grade		
Not recorded	10	12
1	6	6
2	11	17
3	39	34
4	4	5
5	0	0
Surgeon Grade		
Consultant	39	45
Senior StR	25	20
Junior StR	5	9
Core Trainee	1	0
Other	0	0
Closure Method		
Continuous Suture	1	3
Interrupted Suture	3	10
Subcuticular Suture	61	58
Skin Clips	3	3
Drain Placed	7	5

ASA = American Society of Anaesthesiologists; StR = Specialty Training Registrar

4.4.2 Primary Outcome; the Incidence of Surgical Site Infection Within 30 Days of Surgery

Fewer patients in the DACC-coated group had SSI at 30 days than the control group (12/74 (16.22%) and 18/70 (25.71%) respectively; Figure 12). The difference was non-significant (p=0.161, Pearson's χ^2 test). Figure 13 shows the percentage of each group experiencing SSI. This represents an absolute risk reduction (ARR) of 9.5%, a relative risk reduction (RRR) of 36.9% and a number needed to treat (NNT) of 10.5 patients. The crude odds ratio (OR) was 0.559 [95% CI: 0.247, 1.267].

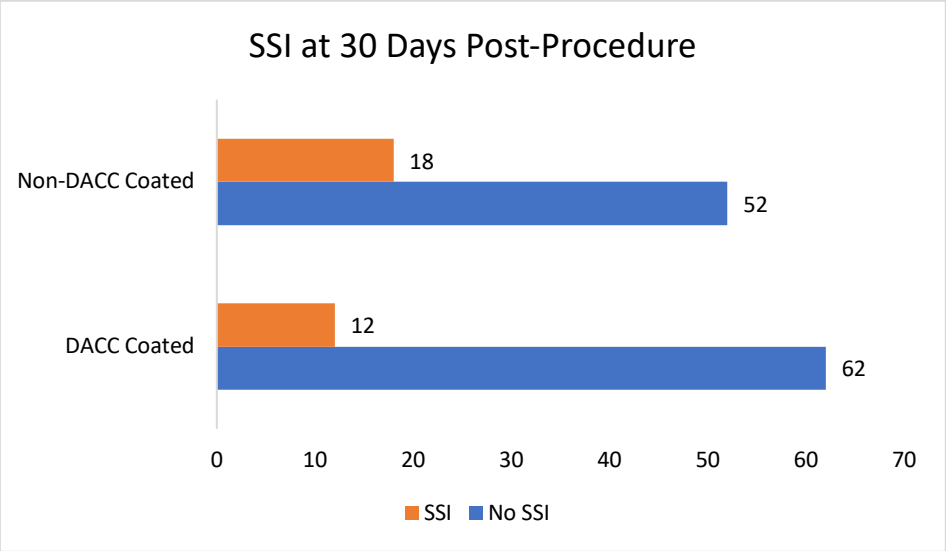


Figure 12 – Number of SSIs at 30 days post-procedure

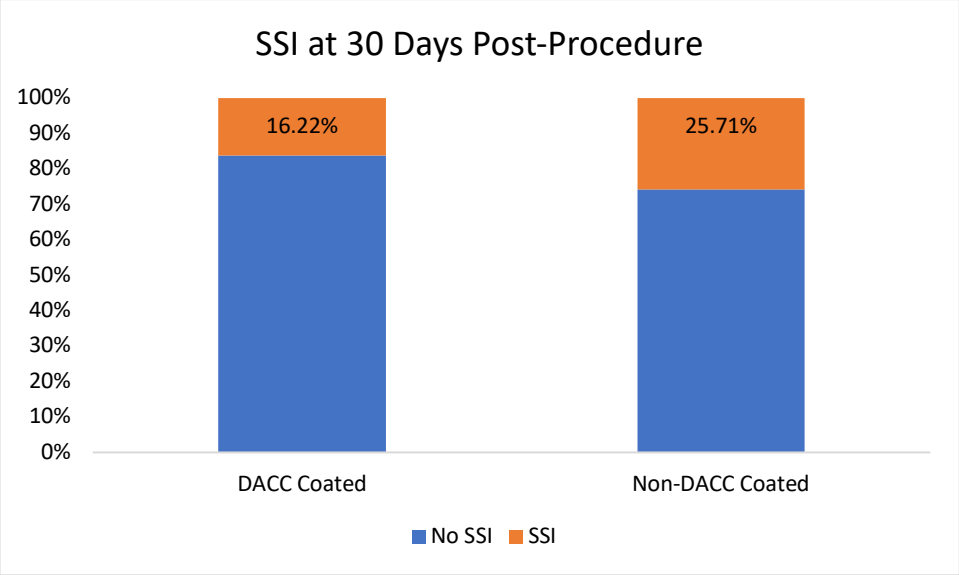


Figure 13 – Percentage of SSI based on dressing allocation

4.4.2.1 SSI rates divided by surgery type

Procedures were grouped into six distinct subtypes. Table 22 outlines the number of SSI in each subtype of surgery performed and figure 14 shows the rates of SSI in each subtype of surgery. There were no significant differences found between groups in each surgery subtype.

Table 22 – Number of SSIs divided by surgery type

Surgery Type	**Randomisation**	**No SSI, *n***	**SSI, *n***	**P =**
Open Abdominal	Non-DACC-Coated	13	1	0.345[ø]
	DACC-Coated	12	0	
Lower Limb Arterial	Non-DACC-Coated	19	10	0.434[ø]
	DACC-Coated	21	7	
Varicose Vein	Non-DACC-Coated	5	1	0.707[ø]
	DACC-Coated	6	2	
Major Limb Amputation	Non-DACC-Coated	4	3	0.696[ø]
	DACC-Coated	5	3	
Renal Dialysis Access	Non-DACC-Coated	7	2	0.156[ø]
	DACC-Coated	8	0	
Other	Non-DACC-Coated	4	1	0.164[ø]
	DACC-Coated	9	0	

[ø]Pearson's χ^2 test. A p-value of <0.05 denotes statistical significance.

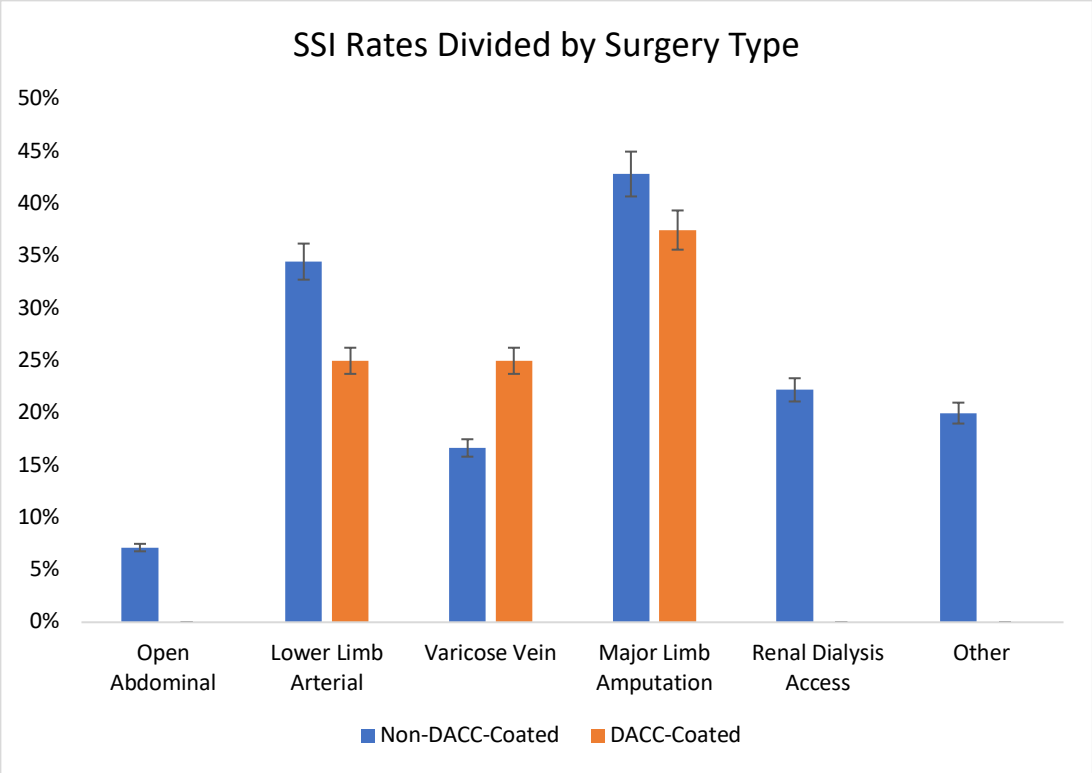


Figure 14 - SSI rates (%) divided by surgery subtype

4.4.2.2 Per-protocol analysis

Due to a relatively large amount of missing outcome data, a per protocol analysis was also performed. Where patients withdrew or died after the POD 30 stage, their data was included in the primary outcome analysis. Table 23 shows the number of SSI at 30 days in each group. The difference in infection rates was non-significant ($p = 0.154$, Pearson's χ^2 test).

Table 23 – Number of SSI at 30 days reflecting missing data

	No SSI (%)	**SSI (%)**	**Unknown (%)**
DACC-Coated	49 (66.2%)	12 (16.2%)	13 (17.6%)
Non-DACC-Coated	40 (57.1%)	18 (25.7%)	12 (17.1%)

4.4.2.3 Factors which may increase the risk of SSI

To assess the effect of other factors on rates of SSI at 30 days post-procedure, study participants were classified as "SSI" or "no SSI" and Pearson's χ^2 test or Independent samples t-tests used to assess for differences between the two groups (Tables 24 to 26). Factors investigated included age, sex, surgery type, smoking status, diabetes, presence or absence of PVD, CVD, respiratory disease and diabetes, and pre-operative serum albumin. Concomitant taking of anticoagulants, steroids (inhaled and oral), NSAIDs and antiplatelet medications were also assessed, as were intraoperative factors such as surgeon grade, ASA grade, closure method and drain placement.

Presence of diabetes, presence of PVD and type of surgery performed were the only factors that had a statistically significant effect on rates of SSI. Of 30 patients who experienced SSI, 14 had diabetes, either diet, tablet or insulin controlled, compared to 29 of 114 who did not experience SSI (p=0.024). In the SSI group, 20 patients had PVD (66.7%) vs 52 in the no SSI group (46.0%), a statistically significant difference (p=0.044). More patients who experienced SSI had lower limb arterial surgery or major limb amputations than those who did not experience SSI (56.7% and 20.0% vs 35.1% and 8.8% respectively, p=0.029). Current or ex-smokers were seemingly less likely to experience infection – 14 patients of the 30 with SSI were current or ex-smokers (60%), in comparison to 93 of the 114 patients without SSI (81.6%) (p=0.012). There were no differences found between groups with respect to other baseline characteristics, including BMI, or concomitant medication use. With regards to intraoperative factors, the only significant difference between the two groups was that more patients in the SSI group had the placement of a drain (26.7%) than in the no SSI group (3.5%) (p<0.001).

Table 24 – Analysis of independent factors that may influence rates of SSI

	No SSI (n=114)	**SSI (n=30)**	***P* =**
Age (years)	63.00	63.73	0.733$^{\Delta}$
Male Sex	61.4%	80.0%	0.057^{ø}
BMI ≥30	29.8%	43.3%	0.160^{ø}
Surgery Type			
Open Abdominal	21.9%	3.3%	
Lower Limb Arterial	35.1%	56.7%	
Varicose Vein	9.6%	10.0%	0.029^{ø**}
Major Limb Amputation	8.8%	20.0%	
Renal Dialysis Access	13.2%	6.7%	
Other	11.4%	3.3%	
Current or Ex-Smoker	81.6%	60%	0.012^{ø**}
Diabetes	25.4%	46.7%	0.024^{ø**}
PVD	46.0%	66.7%	0.044^{ø**}
Pre-Operative Albumin	35.6	35.7	0.867$^{\Delta}$
Respiratory Disease	21.9%	16.7%	0.528^{ø}
Cardiac Disease	40.4%	43.3%	0.768^{ø}

*^{ø}Pearson's χ^2 test. $^{\Delta}$Independent samples t-test. **A p-value of <0.05 denotes statistical significance. SSI = Surgical Site Infection. PVD = Peripheral Vascular Disease.*

Table 25 – Analysis of medications that may influence rates of SSI

Medication	**No SSI (n=114)**	**SSI (n=30)**	***P* =**
Anticoagulation	10.5%	20.0%	0.163^{ø}
Oral Corticosteroid	2.6%	6.7%	0.279‡
Inhaled Corticosteroid	13.2%	10.0%	0.642^{ø}
NSAID	5.3%	3.3%	0.662^{ø}
Antiplatelet	50.0%	60.0%	0.329^{ø}

*^{ø}Pearson's χ^2 test. ‡Fisher's exact test. **A p-value of <0.05 denotes statistical significance. NSAID = Non-steroidal anti-inflammatory.*

Table 26 – Analysis of Intraoperative factors that may influence rates of SSI

	No SSI (n=114)	**SSI (n=30)**	***P* =**
Surgeon Grade			
Consultant	58.8%	56.7%	
Senior StR	30.7%	33.3%	0.953ø
Junior StR	9.6%	10.0%	
Core Trainee	0.9%	0%	
ASA Grade			
Not Recorded	16.7%	10.0%	
1	8.8%	6.7%	0.331ø
2	21.9%	10.0%	
3	47.4%	63.3%	
4	5.3%	10.0%	
Closure Method			
Continuous Suture	2.7%	3.4%	
Interrupted Suture	8.8%	10.3%	0.643ø
Subcuticular Suture	83.2%	86.2%	
Skin Clips	5.3%	0%	
Drain Placement	3.5%	26.7%	<0.001ø**

*øPearson's χ^2 test. **A p-value of <0.05 denotes statistical significance. ASA = American Society of Anaesthesiologists; StR = Specialty Training Registrar.*

4.4.2.4 Controlling for confounding variables

A binomial logistic regression analysis was undertaken to ascertain the effects of various factors, including dressing group allocation, on the likelihood of experiencing SSI. Sex, age, BMI, ASA grade 3 or higher, presence or absence of PVD, diabetes, smoking status, procedure performed and randomisation group were included in the model. The model explained 44.2% (Nagelkerke R^2) of the variance in SSI and correctly classified 86.7% of cases. It indicated that sex, BMI, smoking status, procedure type and drain placement were significant predictors of SSI. Males were 5.85 times more likely to experience SSI and those who had infra-inguinal surgery

were 7.32 times more likely to experience SSI. Those who had a drain placed intraoperatively were 8.56 times more likely to experience SSI. Increasing BMI was associated with an increasing risk of SSI. Randomisation group was not associated with a significant change (OR 0.43 [95% CI: 0.15, 1.24]). Table 27 summarises the results of the logistic regression analysis.

Table 27 – Binomial logistic regression analysis of identified variables associated with an increase in incidence of SSI

					95% CI	
Variable	**Wald**	**df**	**Sig**	**OR**	Lower	Upper
Sex (Male)	6.187	1	0.013*	5.850	1.454	23.530
Age	0.167	1	0.682	1.010	0.963	1.060
BMI	4.765	1	0.029*	1.109	1.011	1.216
Presence of PVD	1.030	1	0.310	2.107	0.500	8.883
Current or Previous Smoker	7.894	1	0.005*	0.144	0.037	0.556
Presence of Diabetes	0.049	1	0.824	1.131	0.381	3.360
Randomisation Group	2.584	1	0.108	0.423	0.148	1.208
ASA grade ≥ 3	0.722	1	0.396	1.742	0.484	6.273
Surgical procedure performed[ø]	6.105	1	0.013*	7.321	1.509	35.515
Placement of a Drain	6.166	1	0.013*	8.560	1.572	46.610

*[ø]Surgical procedure performed is dichotomised into infrainguinal surgery and other vascular surgeries. *denotes statistical significance. df = degrees of freedom; Sig = significance; OR = Odds Ratio; CI = Confidence Interval; ASA = American Society of Anaesthesiologists.*

4.4.2.5 ASEPSIS Scores

When using ASEPSIS alone to diagnose SSI at 30 days, data was available for 90 participants (62.5%). 8 of 39 in the control arm were classed as having SSI, compared to 6 of 51 in the DACC-coated arm (20.5% vs 11.8% respectively; OR 0.517 [95% CI: 0.163, 1.637]; $p = 0.256$, Pearson's χ^2 test).

The distribution of ASEPSIS scores at 30 days and 7 days were compared between groups using the Mann Whitney U test. There was no significant difference in ASEPSIS score between groups at 7 days ($p = 0.726$) or at 30 days ($p = 0.605$). At 30 days, the

median ASEPSIS score in the DACC-coated group was 0 (IQR 10); in the non-DACC-coated group the median ASEPSIS score was 3 (IQR 12). This is shown in Figure 15.

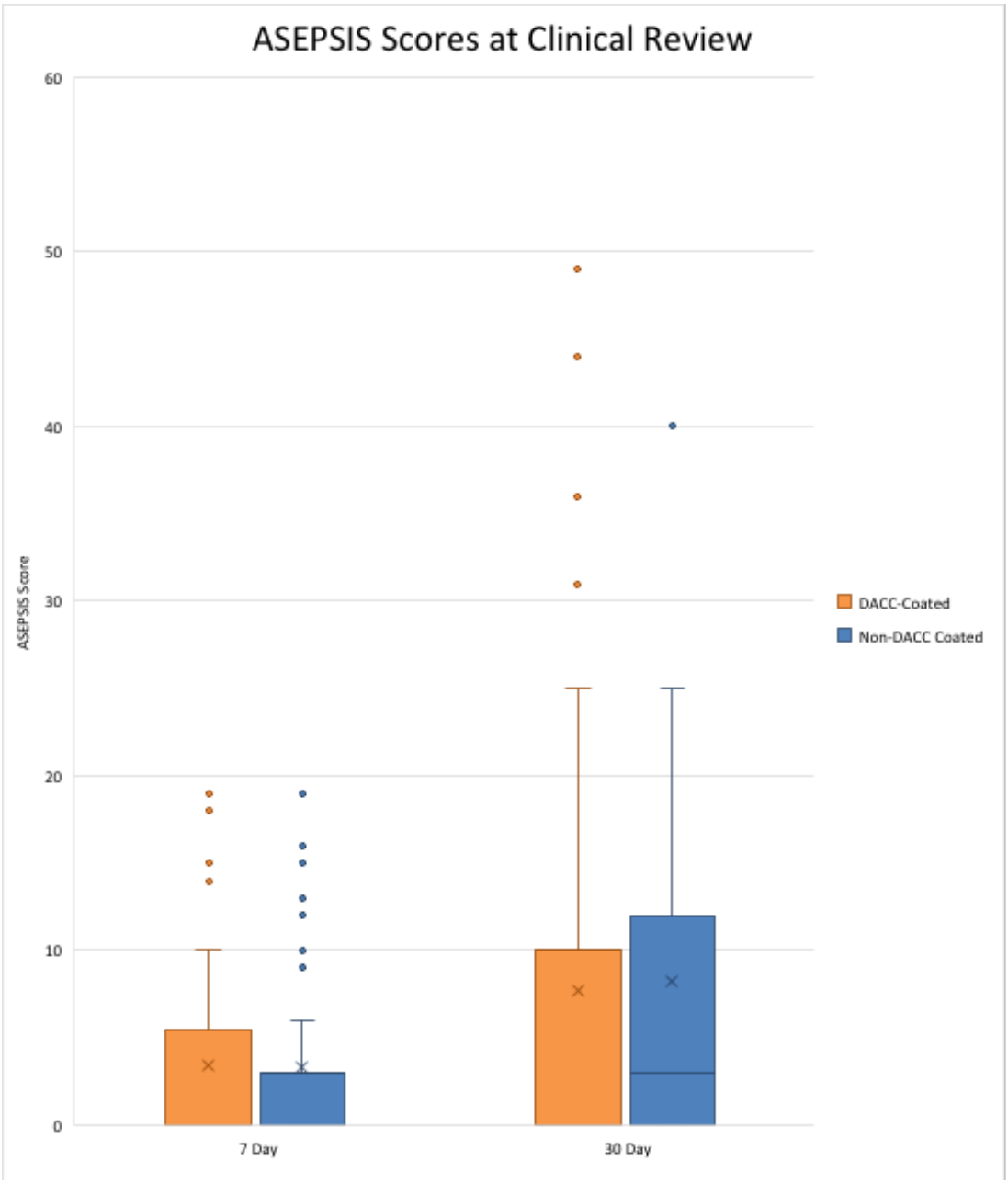


Figure 15 - Box and whisker plot of ASEPSIS scores at clinical review

The bar represents the median; the box represents the inter-quartile range (IQR) and the whiskers represent the values up to twice the inter-quartile range. The dots represent outliers that are more than twice the IQR.

4.4.3 Secondary Outcomes

4.4.3.1 Satisfactory healing within 30 days for all patients

More patients achieved satisfactory healing within the first 30 days in the DACC-coated group than the control group (62.3% vs 50.0%). The difference was non-significant (p = 0.236, Pearson's χ^2 test). Figure 16 shows the rates of satisfactory healing, impaired wound healing and surgical site infection, as defined by ASEPSIS score, within the first 30 days, for those with data available.

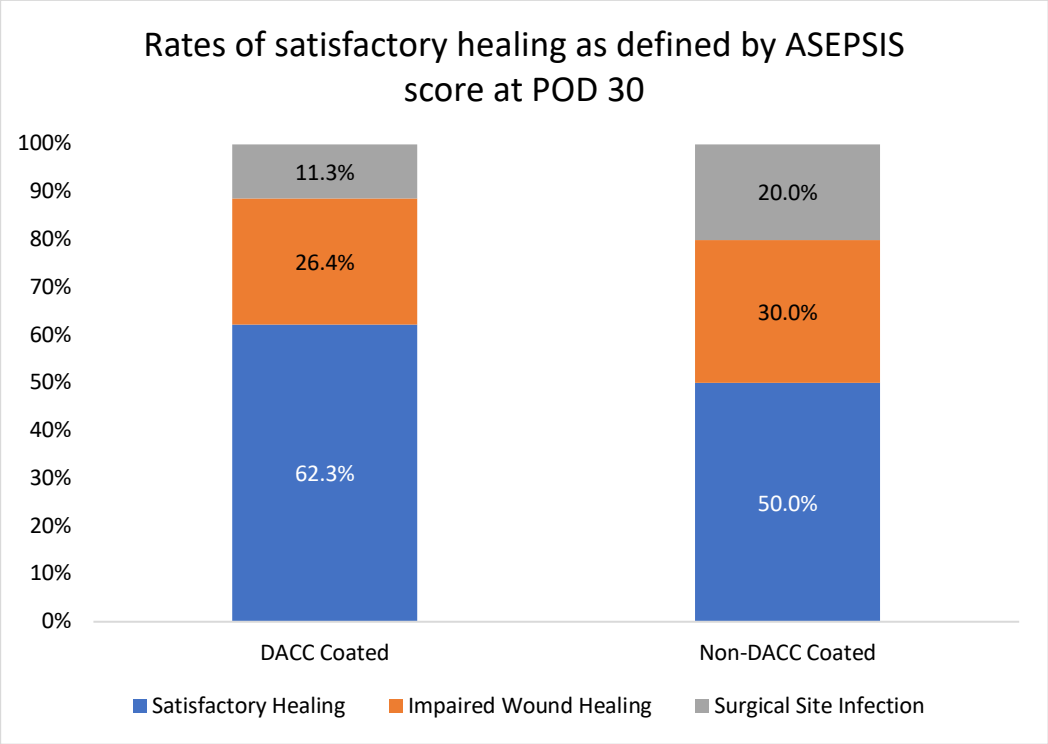


Figure 16 Rates of SSI, IWH and satisfactory healing at POD 30

4.4.3.2 The incidence of SSI at 90 days for procedures involving an implant only

51 patients of the original 144 (35.4%) underwent a procedure involving a prosthetic implant. 38 of these (74.5%) were male, and the group had a mean age of 68.2 (±9.74) years. Table 28 outlines the baseline characteristics of the implant sub-group. Within the 'implant group,' 3 patients were lost to follow up (2 control, 1 intervention) and 2 patients withdrew from the study (1 control, 1 intervention), a combined attrition rate of 9.8%.

Table 28 – Baseline characteristics of the 'implant' subgroup

	Non-DACC-Coated (n = 25)	DACC-Coated (n = 26)
Male	19	19
Female	6	7
Age	68.4 (±9.18)	68.0 (±10.4)
Procedure Performed		
Open abdominal	14	12
Lower limb arterial	10	12
Renal dialysis access	1	1
Other	0	1

In this group, no infections occurred between the POD 30 and POD 90 time-points. There was a non-significant difference in infection rates between the two randomisation groups (p = 0.109, Pearson's χ^2 test). Figure 17 shows the rates of SSI between groups at the 30 and 90 POD points.

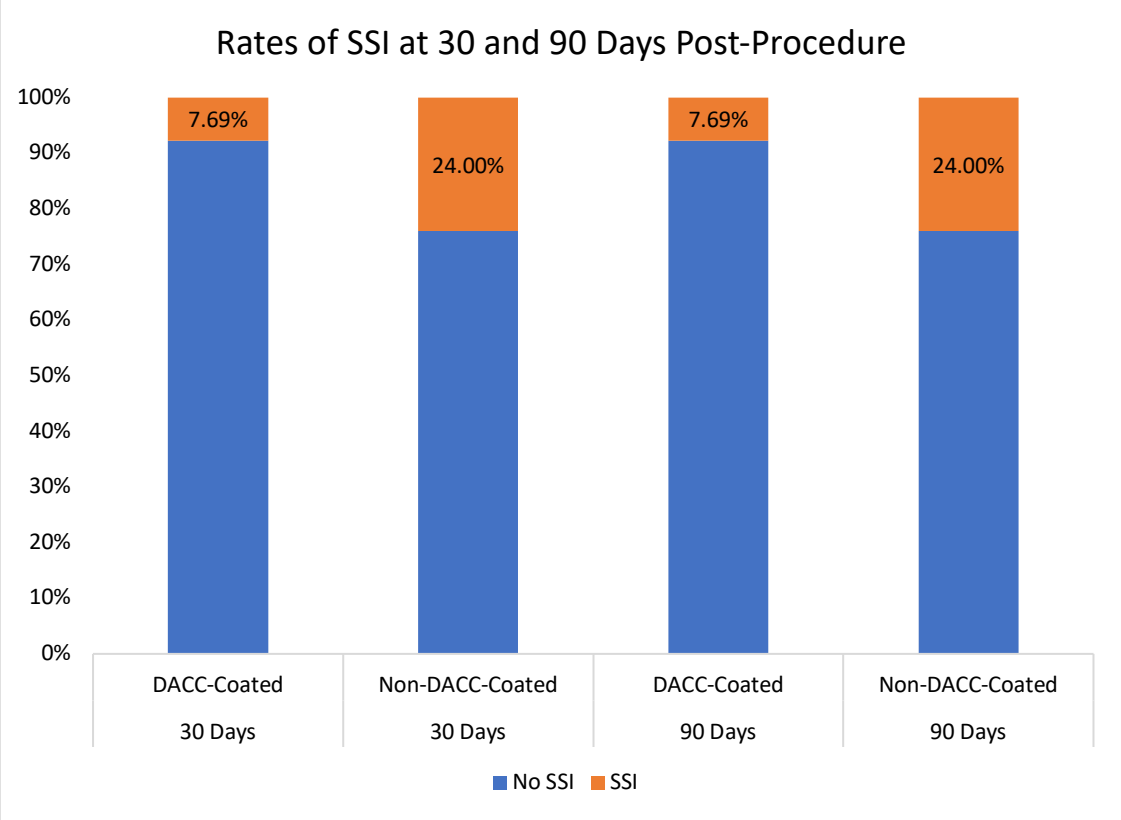


Figure 17 - Rates of SSI at 30 and 90 days for implant-involving surgery only

4.4.3.3 Quality of Life

Two tools to assess QoL were used in this study; the SF-36 utility and the EQ-5D utility, which consists of the EQ-5D questions and the EQ visual analogue score (VAS). Both intragroup and intergroup analysis was carried out between randomisation groups.

4.4.3.3.1 Intragroup Analysis

4.4.3.3.1(a) DACC-Coated Group

In unadjusted analysis, patients demonstrated a significantly changed QoL in 8 of 11 domains of the SF-36 utility. The results are summarised in table 29. No statistically significant differences in QoL were seen in the general health, vitality, and mental health domains. All domains showed an increase in mean score at three months compared to baseline. All domains with the exception of the vitality domain showed an increase in mean score at 30 days compared to baseline.

For EQ-5D, there were no statistically significant differences in any domain (Table 31). There were no significant differences in QoL measured by the EQ-VAS (Table 33).

4.4.3.3.1(b) Non-DACC-Coated Group

In unadjusted analysis, patients demonstrated a significantly changed QoL in only one of 11 domains (health transition) of the SF-36 utility. Results are summarised in table 30. No statistically significant differences were seen in the other domains. At the three-month time point, the physical function, role physical, bodily pain, mental health, health transition, and physical component score domains showed an increase in mean score compared to baseline.

For EQ-5D, only the self-care domain showed a statistically significant difference when compared to baseline. There were no statistically significant differences in any other domains (Table 32). There were no significant differences in QoL measured by the EQ-VAS (Table 34).

Table 29 – Intragroup analysis: QoL indicators (SF-36) at all time points in the DACC-coated group

SF-36 Component		Baseline (n = 53)			7 days (n = 40)			30 Days (n = 37)			3 Months (n = 32)			*P* =
		Mean	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	
	PF	40.18	31.00	30.00	35.50	27.78	25.00	57.02	29.96	60.00	61.15	28.90	75.00	0.001**
	RP	37.85	32.04	31.25	30.16	23.89	28.13	41.89	32.37	43.75	58.79	28.96	56.25	0.034**
	BP	44.34	31.21	32.50	35.88	27.79	31.25	49.86	28.30	45.00	67.03	26.29	72.50	<0.001**
	GH	46.79	25.17	45.00	47.13	22.70	50.00	51.76	25.93	50.00	57.18	22.79	55.00	0.247
	Vit	40.45	22.92	37.50	39.22	21.32	43.75	39.53	21.20	43.75	51.02	18.94	56.25	0.074
	SF	50.71	32.10	50.00	46.88	28.83	50.00	55.40	34.68	50.00	77.73	24.74	87.50	0.040**
	RE	58.96	36.21	58.33	54.37	39.49	50.00	62.84	36.78	58.33	77.60	28.75	95.84	0.032**
	MH	60.00	20.87	60.00	60.88	20.63	60.00	67.97	21.29	70.00	81.72	13.89	82.50	0.079
	HT	38.21	18.08	50.00	41.93	23.63	50.00	50.00	29.46	50.00	60.94	25.35	50.00	0.048**
	PCS	*42.30*	*25.73*	*37.19*	*36.79*	*19.56*	*33.91*	*50.14*	*22.61*	*53.13*	*61.03*	*21.47*	*62.03*	*<0.001***
	MCS	*52.53*	*23.35*	*50.31*	*50.40*	*22.04*	*50.56*	*56.44*	*23.12*	*58.65*	*72.11*	*15.93*	*72.14*	*0.007***

***denotes statistical significance (P < 0.05). A Friedman's two-way ANOVA test was used to obtain P values. S.D. = Standard Deviation. PF = Physical function. RP = Role Physical. BP = Bodily Pain. GH = General Health. Vit = Vitality. SF = Social Function. RE = Role Emotional. MH = Mental Health. HT = Health Transition. PCS = Physical Component Score. MCS = Mental Component Score.*

Table 30 – Intragroup analysis: QoL indicators (SF-36) at all time points in the non-DACC-coated (control) group

SF-36 Component		Baseline (n = 44)			7 days (n = 30)			30 Days (n = 27)			3 Months (n = 25)			*P* =
		Mean	S.D.	Median	Mean	S.D.	Median	Mean	S.D.	Median	Mean	S.D.	Median	
	PF	47.95	34.73	45.00	46.33	34.06	45.00	54.07	31.41	50.00	56.80	29.08	50.00	0.941
	RP	47.16	36.68	53.12	46.25	35.07	50.00	44.44	31.41	43.75	51.25	32.87	50.00	0.356
	BP	52.33	32.27	50.00	46.75	31.19	45.00	57.69	28.50	55.00	59.30	32.78	57.50	0.125
	GH	51.02	27.99	55.00	46.84	24.90	42.50	55.56	25.51	60.00	49.60	28.57	50.00	0.442
	Vit	48.84	27.72	53.13	43.75	24.95	43.75	47.68	25.66	50.00	45.00	24.14	43.75	0.887
	SF	65.06	33.63	75.00	59.17	32.32	62.50	60.19	33.80	62.50	62.50	31.87	62.50	0.382
	RE	69.70	40.27	100	63.06	38.20	66.67	69.14	35.72	75.00	62.67	35.53	75.00	0.192
	MH	69.89	22.27	75.00	64.50	23.13	60.00	73.52	21.39	75.00	70.20	24.09	75.00	0.682
	HT	38.07	24.40	50.00	44.17	27.61	50.00	46.30	29.17	50.00	44.00	30.00	50.00	0.015**
	PCS	*49.96*	*28.63*	*48.60*	*46.54*	*26.64*	*52.82*	*52.94*	*23.65*	*51.88*	*54.24*	*27.11*	*51.56*	*0.421*
	MCS	*63.37*	*26.88*	*73.44*	*57.62*	*25.43*	*60.52*	*62.63*	*25.58*	*65.42*	*60.09*	*25.72*	*65.31*	*0.766*

***denotes statistical significance (P < 0.05). A Friedman's two-way ANOVA test was used to obtain P values. S.D. = Standard Deviation. PF = Physical function. RP = Role Physical. BP = Bodily Pain. GH = General Health. Vit = Vitality. SF = Social Function. RE = Role Emotional. MH = Mental Health. HT = Health Transition. PCS = Physical Component Score. MCS = Mental Component Score.*

Table 31 – Intragroup analysis: QoL indicators (EQ-5D) at all time points for the DACC-coated group

		Percentage (%) of individuals reporting no problems				
		Baseline (n=53)	7 Days (n=39)	30 Days (n=35)	3 Months (n=29)	***P* =**
EQ-5D Component	**Mobility**	24.9%	33.3%	51.4%	44.8%	0.748
	Self-Care	69.8%	63.2%	82.9%	93.1%	>0.999
	Usual Activity	32.1%	25.6%	34.3%	41.4%	0.934
	Pain/Discomfort	20.8%	23.1%	42.9%	44.8%	0.147
	Anxiety/Depression	59.6%	82.1%	82.9%	86.2%	0.284

***denotes statistical significance (P < 0.05). A related samples Cochrane's Q test was used to obtain P values*

Table 32 – Intragroup analysis: QoL indicators (EQ-5D) at all time points for the non-DACC-coated group

		Percentage (%) of individuals reporting no problems				
		Baseline (n=44)	7 Days (n=31)	30 Days (n=28)	3 Months (n=25)	***P* =**
EQ-5D Component	**Mobility**	38.6%	35.5%	39.3%	36.0%	0.261
	Self-Care	73.3%	61.3%	85.7%	62.5%	0.029**
	Usual Activity	42.4%	38.7%	46.4%	43.5%	0.494
	Pain/Discomfort	29.5%	22.6%	32.1%	36.0%	0.875
	Anxiety/Depression	73.3%	71.0%	75.0%	70.8%	0.392

***denotes statistical significance (P < 0.05). A related samples Cochrane's Q test was used to obtain P values*

Table 33 – Intragroup analysis – EQ-VAS scores at all time points for the DACC-coated group

Baseline (n = 51)			**7 days (n = 39)**			**30 Days (n = 37)**			**3 Months (n = 30)**			***P* =**
Mean	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	
59.72	22.80	60.00	64.59	19.26	70.00	68.21	22.98	75.00	76.30	13.46	80.00	0.088

***denotes statistical significance (P < 0.05). A Friedman's two-way ANOVA test was used to obtain P values. S.D. = Standard Deviation*

Table 34 – Intragroup analysis – EQ-VAS scores at all time points for the non-DACC-coated (control) group

Baseline (n = 41)			**7 days (n = 31)**			**30 Days (n = 28)**			**3 Months (n = 25)**			***P* =**
Mean	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	*Mean*	*S.D.*	*Median*	
63.46	27.43	68.00	69.29	17.99	70.00	70.57	23.18	80.00	68.24	27.00	82.00	0.348

***denotes statistical significance (P < 0.05). A Friedman's two-way ANOVA test was used to obtain P values. S.D. = Standard Deviation*

4.4.3.3.2 Intergroup Analysis

At each time point, a Mann-Whitney U test was used to compare the QoL scores between groups for the SF-36. Only the RP at 7 days (p = 0.027) and HT at 3 months (p = 0.021) had statistically significant differences between groups. There were no other statistically significant differences in any domain of the SF-36 at any time point (Table 35).

Table 35 - Intergroup analysis: Comparison between groups at each time point for each domain of the SF-36

		P =		
		7 Days	30 Days	3 Months
SF-36 Component	**PF**	0.159	0.713	0.589
	RP	0.027**	0.692	0.348
	BP	0.073	0.324	0.403
	GH	0.830	0.549	0.321
	Vit	0.492	0.190	0.211
	SF	0.100	0.583	0.076
	RE	0.283	0.564	0.089
	MH	0.551	0.266	0.070
	HT	0.626	0.683	0.021**
	PCS	0.103	0.659	0.257
	MCS	0.174	0.229	0.103

***denotes statistical significance (P < 0.05). A Mann-Whitney U test was used to obtain P values. PF = Physical function. RP = Role Physical. BP = Bodily Pain. GH = General Health. Vit = Vitality. SF = Social Function. RE = Role Emotional. MH = Mental Health. HT = Health Transition. PCS = Physical Component Score. MCS = Mental Component Score.*

For EQ-5D, the only significant difference between groups was seen in the self-care domain at the 3-month time point. All other differences between groups were non-significant (Table 36).

There were no significant differences between groups in the EQ-VAS at any time point.

Table 36 – Intergroup analysis: Comparison between groups at each time point for each domain of the EQ-5D

		P =		
		7 Days	30 Days	3 Months
EQ-5D Component	**Mobility**	0.851	0.337	0.510
	Self-Care	0.873	0.758	0.006**
	Usual Activity	0.242	0.328	0.879
	Pain/Discomfort	0.961	0.384	0.510
	Anxiety/Depression	0.273	0.444	0.170

*All P-values derived using Pearson's χ^2 test. **A p-value of <0.05 denotes statistical significance.*

4.4.3.3.3 Quality of life between those with SSI and those without

QoL was compared between those who experienced SSI within the study period and those who did not, using the SF-36 PCS, the SF-36 MCS, and the EQ-5D VAS. Comparisons were conducted using Friedman's two-way ANOVA tests. In those who did not experience SSI, there was a significant improvement in QoL as measured by SF-36 PCS ($p < 0.001$), SF-36 MCS ($p = 0.22$) and EQ-VAS ($p = 0.028$) from baseline. In those who experienced SSI, there were no significant changes observed in SF-36 PCS ($p = 0.615$), SF-36 MCS ($p = 0.494$) or EQ-VAS ($p = 0.580$) over the course of the study (Figures 18 to 20).

Figures 18 to 20 – Plots outlining QoL between those who experienced SSI within the study period and those who did not. The points represent the mean score at each time point. The bars represent the 95% confidence interval for the mean.

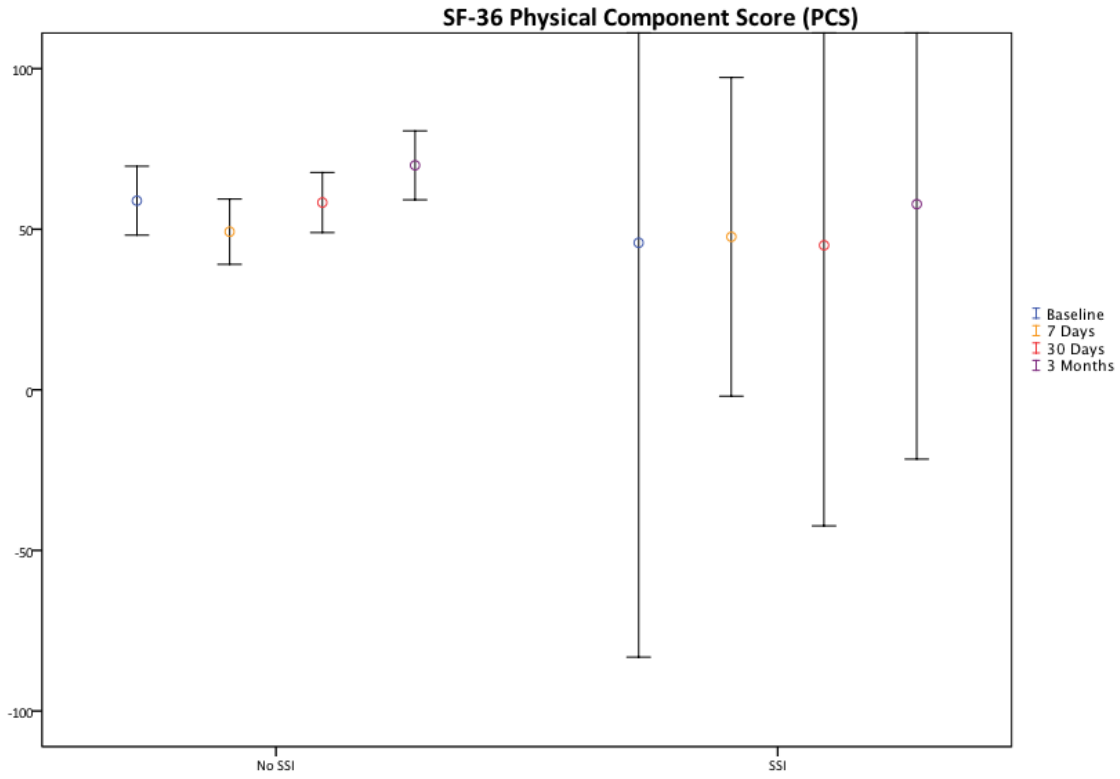


Figure 18 - Quality of Life, SF-36 PCS, in those with SSI and those without

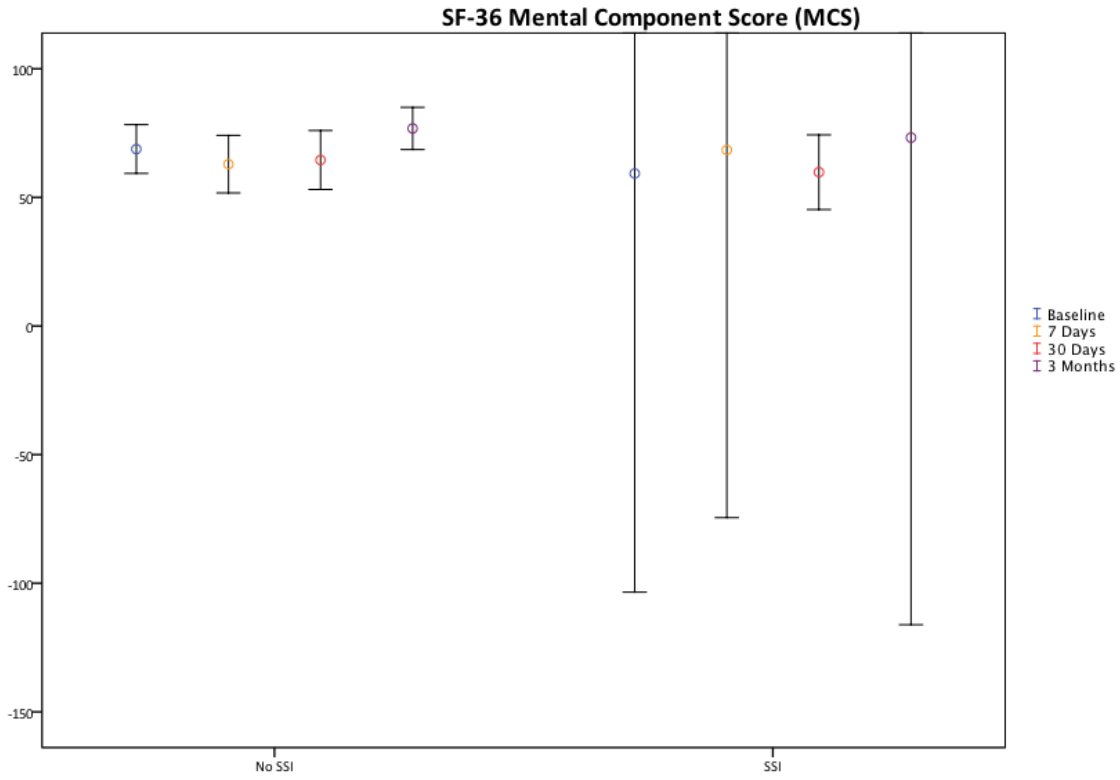


Figure 19 - Quality of Life, SF-36 MCS, in those with SSI and those without

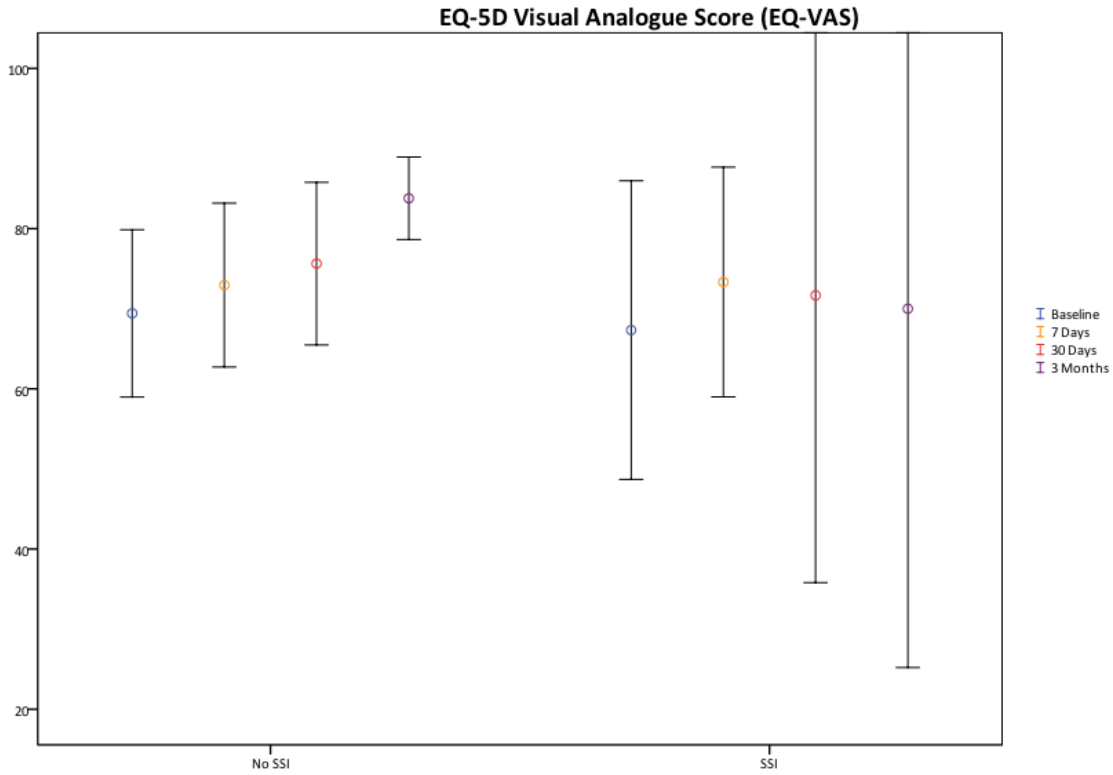


Figure 20 - Quality of Life, EQ-VAS, in those with SSI and those without

4.4.3.4 Resource use; readmission, reintervention, antibiotic use, inpatient days

In total, 6 patients were readmitted to hospital as a consequence of SSI, 2 in the non-DACC coated group and 4 in the DACC-coated group (2.9% and 5.4% respectively). There was a non-significant difference in readmission rates between groups (p = 0.444, Pearson's χ^2 test).

3 patients in total required re-intervention (return to theatre) as a result of SSI. All three were in the DACC coated group (4.1%). Re-intervention rates between dressing groups was not statistically significant (p = 0.245, Fisher's exact test).

With regards to antibiotic use, in those who experienced SSI in the control group, 10 patients required oral antibiotics within 30 days of their procedure and 7 required IV antibiotics. In the DACC-coated group, 7 required oral antibiotics, and 5 IV. The difference was not statistically significant (Table 37).

Table 37 – Further treatment required by those with SSI

	DACC-Coated (n = 74)	**Non-DACC-Coated (n = 70)**	***P* =**
Number of patients with SSI requiring oral Abx (%)	7 (9.46%)	10 (14.29%)	0.370[ø]
Number of patients with SSI requiring IV Abx (%)	5 (6.76%)	7 (10%)	0.481[ø]
Number of patients with SSI requiring readmission (%)	4 (5.40%)	2 (2.86%)	0.444[ø]
Number of patients with SSI requiring return to theatre (%)	3 (4.1%)	0 (0%)	0.245[‡]

*[ø]Pearson's χ^2 test. [‡]Fisher's exact test. **A p-value of <0.05 denotes statistical significance. SSI – Surgical site infection, Abx – Antibiotics, IV - Intravenous*

Total number of inpatient hospital days was calculated for patients who experienced SSI, and compared between groups based upon their dressing allocation (Figure 21). The median number of inpatient days in the DACC-coated group was 10 days (IQR 3.25-18.75). The median number of inpatient days in the control group was 11 days (IQR 3.75-21). There was no significant difference between the two groups in terms of total number of hospital inpatient days (p = 0.787, Mann-Whitney U test).

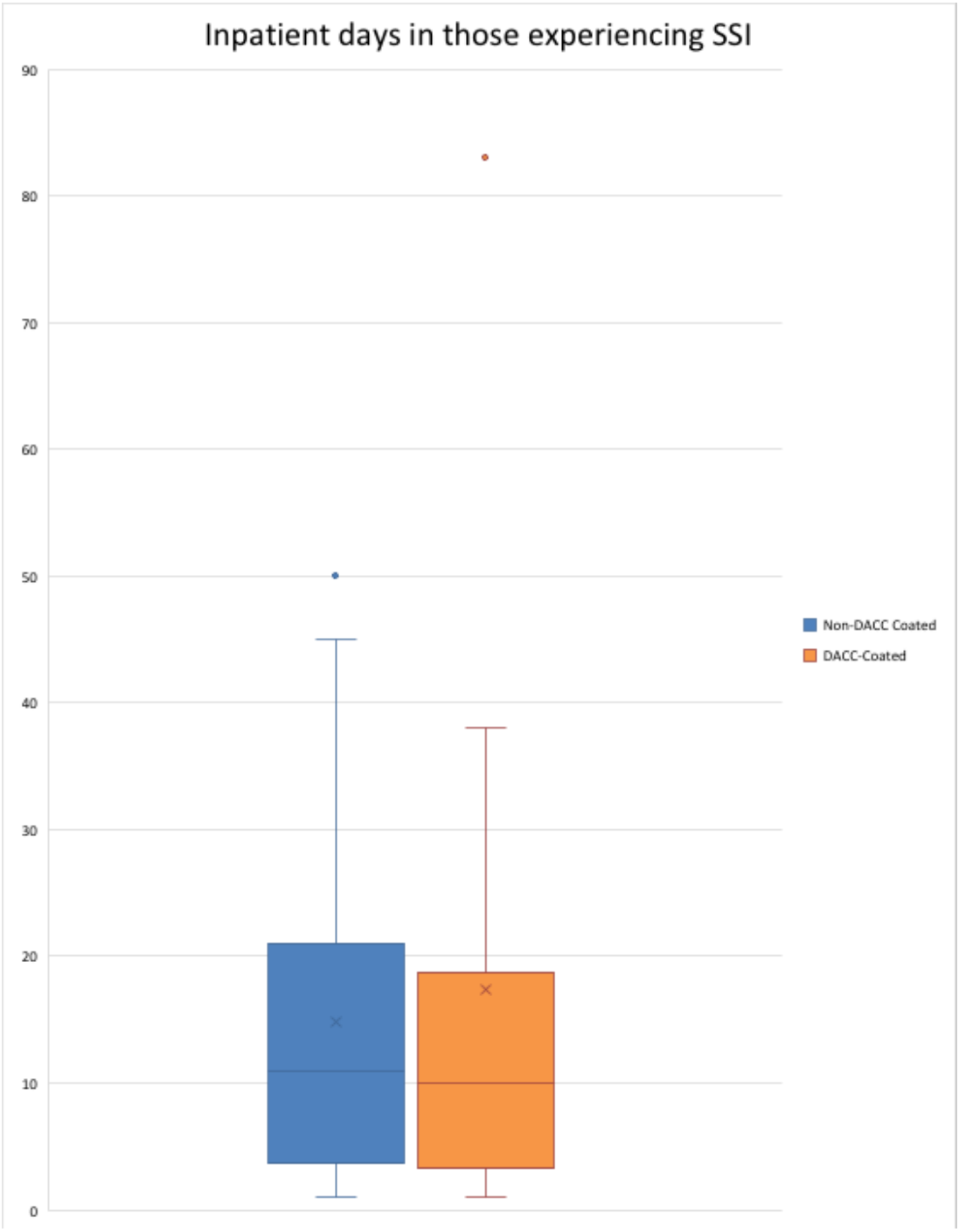


Figure 21 - Box and whisker plot showing total number of hospital days in those experiencing SSI between dressing types

The bar represents the median; the box represents the inter-quartile range (IQR) and the whiskers represent the values up to twice the inter-quartile range. The dots represent outliers that are more than twice the IQR.

4.4.3.5 Time to return to work/normal activity

For time to return to work or normal daily activities, data was available for 101 patients, of which 64 had returned to work within the follow-up period (63.37%).

There was no significant difference in time to return to work between randomisation groups (p = 0.923). Figure 22 shows a Kaplan Meier plot of cumulative time to return to work between randomisation groups.

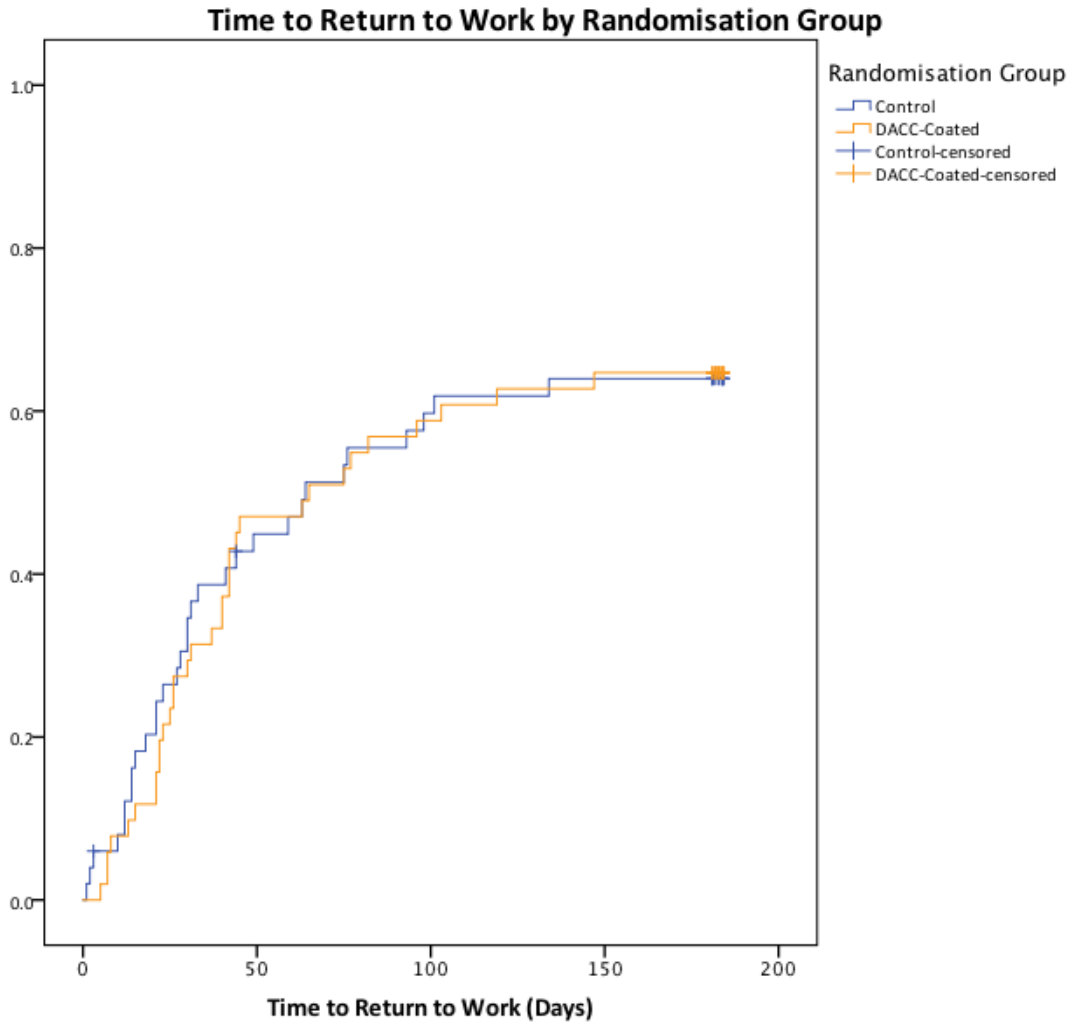


Figure 22 - Kaplain Meier plot showing time to return to work within the study period

Time to return to work was also compared between those who experienced SSI within the study period and those who did not. 69.6% of those with SSI had not returned to work or normal activities within the study period, in comparison to 26.9% of those without infection. There was a statistically significant difference between these two groups when comparing time to return to work/normal activity (p < 0.01). This is shown in figure 23.

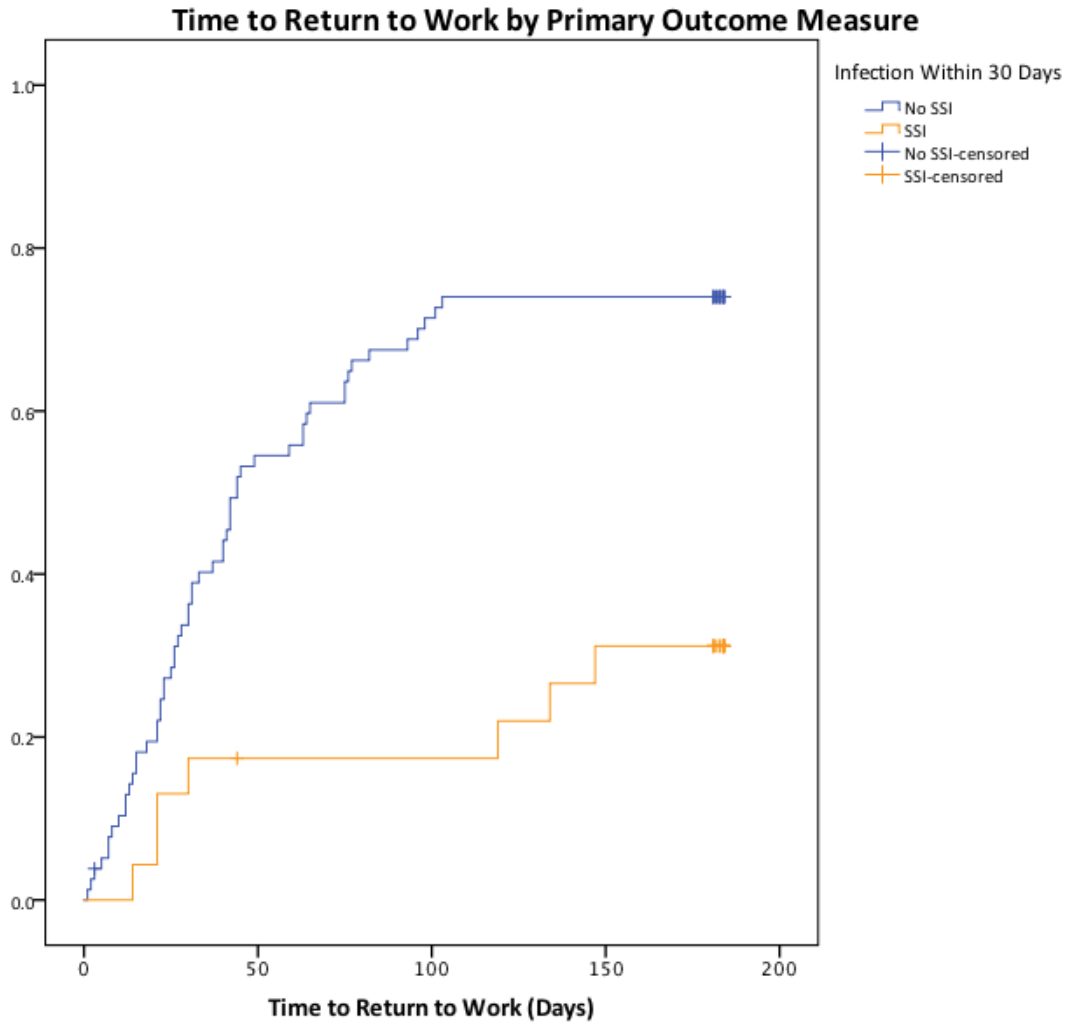


Figure 23 - Kaplan Meier plot of time to return to work/normal activity comparing SSI/No SSI

4.4.3.6 30-Day and 6 Month Mortality

2 patients (1.39%) passed away within 30 days of their index procedure, 1 patient in the DACC-coated group (1.35%) and 1 patient in the control group (1.43%). This difference was non-significant (Fisher's exact test).

5 patients (3.47%) passed away within 6 months of their index procedure; 2 patients in the DACC-coated group (4.05%) and 3 patients in the control group (4.29%). There was no significant difference in 6-month survival between groups (p = 0.705). Figure 24 shows a Kaplan Meier plot of cumulative survival at 6 months post procedure.

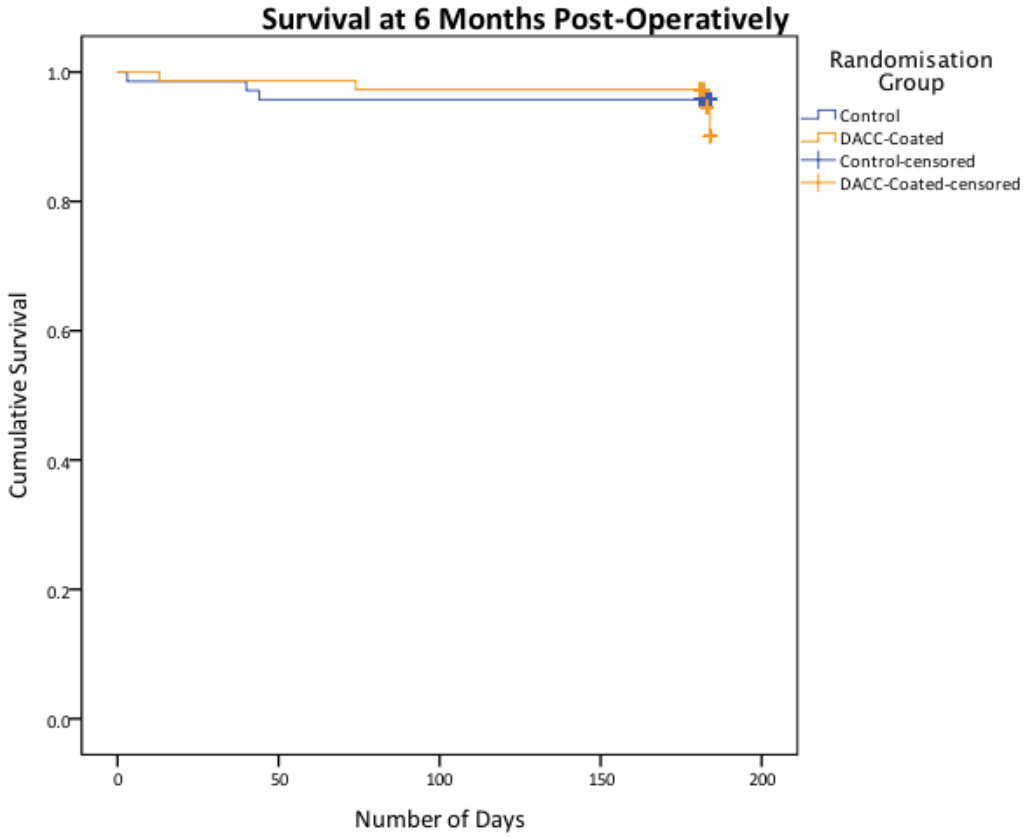


Figure 24 - Kaplan Meier plot of cumulative survival at 6 months post procedure

4.5 Discussion

Dressings coated with DACC, which acts to bind bacteria at the skin surface,[136] have shown promise in reducing rates of SSI and wound infections in general.[165, 183] This early clinical evidence is supported by positive *in vitro* evidence.[136, 144] However, evidence for the use of any dressing in reducing SSI is limited, and at present no single dressing is indicated or recommended for the prevention of SSI in primarily closed wounds.[75, 103, 134] To date, only a single RCT has been conducted investigating the use of DACC-coated dressings as primary prevention of SSI,[165] which was at a high risk of bias due to the methodology employed. Large multi-centred RCTs often fail to recruit or retain participants,[177] and a pilot study has the potential to inform, and improve, the design and conduct of a large scale RCT, and occasionally inform about likely outcomes.[178] The aim of study three, therefore, was to examine the feasibility of delivering a large scale RCT investigating the effect of DACC coated dressings upon rates of SSI within vascular surgery, by conducting a pilot study. In doing so, we set out to examine both the feasibility and the clinical effectiveness of the intervention in question.

4.5.1 The Feasibility of Conducting a Full Randomised Controlled Trial

This study provided a number of important observations that may influence the design or conduct of any large scale, multi-centred RCT. Whilst eligibility and recruitment rates were high, retention and questionnaire response rates were poor, and strategies to improve these should be explored.

4.5.1.1 Eligibility and recruitment

At 72.51%, eligibility for the trial was high. Eligibility for clinical trials often varies according to the trial being performed, with one review of 41 studies estimating an average exclusion rate of 73%.[184] In part, the high eligibility rate seen in this trial may be due to relatively few exclusion criteria. Strict inclusion criteria may lead to a study population that is non-representative of the disease population, leading to poor external validity of a study.[185, 186] In our study, 29.9% of participants had diabetes mellitus, 50.3% of patients had PAD, and 41% had comorbid cardiac disease. In the literature, rates of diabetes in open vascular surgery are estimated at 26.5% – 41.5%

(as high as 49% in those with critical limb ischaemia), PVD at 55.77%, and cardiac disease 37.0%.[88, 187, 188] This suggests that patients recruited to this trial are representative of the wider population of those undergoing vascular surgical procedures.

Of the patients screened in this trial, 43.5% were subsequently randomised. This is, in fact, significantly higher than the 10% quoted in one review of studies.[185] Patients were recruited at a median rate of 10 per month – a review of trials funded and published by the United Kingdom Health Technology Assessment (HTA) Programme estimated overall recruitment to RCTs to be 0.92 patients per centre per month.[189] This was, however, a combination of drug trials, device trials and intervention trials, covering both single and multi-centre trials. The higher than average recruitment rate of this trial may again be reflective of the high eligibility rates, a result of the wide inclusion and exclusion criteria.

Patients not wishing to take part in research, or patients who were unable or unwilling to re-attend hospital for additional clinical visits made up over half of eligible patients who were subsequently not recruited. Travel problems, additional appointments, and additional costs to patients, have all been identified as barriers to participation in clinical research.[189-192] In addition, some patients may not wish to trial 'experimental' treatment, and may not wish to undergo the process of randomisation,[193-196] both were reasons given by patients screened as part of this trial who declined to participate. Whilst some of these may be unavoidable, amending follow up procedures may yield improved recruitment, as over 40% of eligible patients not recruited cited perceived difficulty or undue burden in adhering to the prescribed follow up arrangements as a reason for not entering the trial.

4.5.1.2 Study retention – mortality, withdrawal, follow-up and questionnaire return rates

Mortality during the study follow-up period was 4.86%, with 1.39% mortality within the 30-day period required for the measurement of the primary endpoint. In other clinical trials in patients undergoing vascular surgery, mortality rates vary between 8%[197] and 3%,[88] consistent with the findings of this study.

In total, sixteen participants (11.1%) withdrew from the trial during the follow-up period, and eleven participants (7.64%) were lost to follow-up. This gave a combined attrition rate (along with mortality) of 22.3%. Attrition rates in clinical trials may vary between 5% and 70%.[198] In clinical trials examining SSI, attrition rates have been reported as low as 1.8%,[199] 1.2%,[200] and 1%.[201] However, these were studies conducted in clean contaminated general surgery – patients who are not necessarily as co-morbid as patients undergoing vascular surgery, or have problems such as lower limb bypass or amputation surgery which may impact upon mobility and the ability to travel to hospital appointments. In contrast, the median attrition rate seen in HTA funded trials in the UK was 11%, with at least one trial reporting a retention rate as low as 23%.[189]

Patients in our study were asked to complete QoL questionnaires at each study visit, and again at 3 months post-operatively. Completion at baseline was not 100%. This may be due to a number of factors which would need to be addressed in future studies. Firstly, a number of questionnaires were returned partially incomplete, or incorrectly completed by participants, which led to them being deemed incomplete in a dichotomous analysis. Secondly, participants were often asked to complete questionnaires the night before, or the morning of, a procedure. In such instances, compliance may be low due to the stress of an impending operation. Response rates then fell throughout the trial for all three QoL questionnaires. By the 3-month mark, around 50% of recruits returned a fully completed set of QoL questionnaires.

Retention to clinical studies and maximising data return is becoming a focus of attention of trial methodologists, with a recognition that recruitment, rather than retention, has potentially been the prime target for study investigators in the past.[202] It is estimated that almost 30% of trials encounter missing data due to patients not attending study visits, and over 80% of trials have participants that subsequently withdraw from the trial following randomisation.[203] Both of these are phenomena encountered during our study, and the quality of any large RCT based on our design will likely be adversely affected by the attrition rate observed. It has been shown that offering incentives to patients improves study retention and response rates,[204] and that the ability to offer incentives may help study investigators feel more confident

and comfortable maintaining contact with participants and subsequently more motivated to continue to pursue data.[202, 205]

The consequences of an attrition rate of over 20%, as seen in this pilot study, may be stark – the significance of results may change based on how missing data is handled.[206] An attrition rate of over 20% may seriously compromise study validity,[207] and so strategies to improve retention should be investigated thoroughly before proceeding to upscaling the current study design. In addition, participants who attend one but not both study visits have not been counted in the definition of 'attrition' – in this study, for example, only 63% or participants attended a clinical review at POD 30±3, though primary outcome data was available for 82.6% of participants. This is less than the 89% seen in HTA funded trials.[189] One strategy which has been postulated to improve study retention is the increased or improved use of technology during a clinical trial,[208] both through improving tracking of participants and providing a communication medium and reminders. In particular, studies have already begun to examine the use of technology in trials investigating SSI and wound assessments across the globe,[209, 210] in varying specialties,[211-213] and in routine clinical practice.[214-217] Combining this growing area of interest with established methods of improving follow up such as offering incentives may improve study retention to a more acceptable level.

One cohort of patients in our study who had sub-optimal rates of appointment attendance were those undergoing dialysis access surgery, with an average attendance of 44%. By definition, these patients will have multiple hospital appointments and admissions,[218, 219] and given that their overall rate of SSI was low relative to the overall infection rate seen in the study (11.8%), it is plausible that they would not be motivated to attend yet more appointments for a research trial when their perceived benefit was minimal. It may benefit the outcome of a larger trial to either incentivise attendance/response, as outlined above, or add renal dialysis access surgery to the exclusion criteria of the trial.

More patients were available for follow up between 5 and 7 days than at 30 days. This is likely because a number of procedures, namely open abdominal and lower

limb amputation, carry with them a longer hospital stay post-procedure, and such patients were followed up whilst still a hospital inpatient. Indeed, participants undergoing these procedures had a follow-up rate of 84.6% and 81.3% respectively at 7 days, higher than the average of 72.5% at this time point, though still potentially sub-optimal.

4.5.1.3 Suitability of the assessment methods

The ASEPSIS scoring system, used to identify SSI in post-surgical wounds, has been shown to be reliable and related to patient outcomes.[113, 114, 169] However, the ASEPSIS score remains only one of a number of definitions of SSI, and our study combined the use of ASEPSIS and CDC definitions of SSI.[73, 74] When these two tools are compared, it has been shown that more than twice as many wounds may be classified as infected by only one tool as classified as infected by both.[115] In our study, the benefit to using both definitions was to improve the number of patients for which primary outcome data was available, as ASEPSIS requires a clinical review, whereas the CDC definition may be derived from clinical notes. However, there was a disparity between rates of SSI when ASEPSIS alone was used when compared with the ASEPSIS and CDC definitions combined (16.1% vs 21.0% respectively). This disparity may represent the diagnosis of SSI in the community by General Practitioners (GPs), or may represent the under-diagnosis of SSI by the ASEPSIS tool (Wilson *et al.* observed that 42% of wounds classified only as IWH by ASEPSIS were classified as infected by the CDC definition of SSI[115]). Further still, evidence suggests that both tools used in our study may be inadequate for the diagnosis of SSI following discharge, as they were primarily designed for use in hospital.[117] Patient self-diagnosis of wound infection, however, is unreliable,[220, 221] and a reliance on this for the purposes of collecting data on SSI may lead to a widespread over- or under-reporting of outcomes. Data retrieval from existing computer systems has been shown to be an effective method of collecting data on SSI, however such infrastructure does not yet exist in the primary investigation site of this study.[222] To achieve data that accurately reflects true SSI rates, a combination of assessment methods, involving searching existing computerised data for GP attendances or antibiotic prescriptions, telephone consultations, validated questionnaire use and targeted clinical review, should be

used.[117, 221, 222] Several study groups are currently designing, or validating, novel methods for the follow-up of patients post-discharge which aim to increase the capture rate of data on SSI in both research trials and clinical practice, including the use of tools which can be completed by non-clinical practitioners.[117, 223]

4.5.1.4 Suitability of the trial treatments

Compliance with trial treatments, i.e. the application of the correct dressing for the duration of wound healing, was around 88% across the trial. For some, trial dressings became inadequate due to the condition of the wound. For example, heavily exuding wounds may require alginate or hydrofibre dressing, lest they become uncomfortable, macerated, and impact QoL.[224] Neither the control nor the trial intervention are suitable for such a wound, and so a non-trial dressing is required for the best interest of the patient, as happened in 3 patients in our pilot study. Other studies allow for a non-protocol dressing after the primary endpoint has been reached,[225] however in some, data collection ceases if a deviation from protocol occurs.[226] In this pilot study, data collection continued despite deviations from protocol, and no restrictions were placed on patients' dressings following the diagnosis of SSI. Therefore, it is the authors' recommendation that a strategy where the allocated dressing is adhered to up to the point of the primary outcome (i.e. SSI), followed by a thorough record of any additional dressings used, should be implemented in the protocol of this or any subsequent trials.

In nine patients in the pilot study, wounds were dressed with the wrong dressing, with no clear rationale behind the change. Adherence to the treatment allocation in a trial examining wound dressings may often be problematic, especially as a lack of clear evidence in wound care leads to a myriad of options for the management of wounds,[227] and at least one ongoing clinical trial has taken the novel step of applying temporary tattoos to the skin to encourage dressing compliance.[225] In order to improve the validity of any future study, measures should be taken to both account for the limitations of the trial dressings within the study protocol, and to improve compliance with dressing allocation.

4.5.1.5 Suitability of the data collection tools and methods

In this study, data was collected in paper CRFs, with each participant having their own CRF. Paper CRFs are bulky and require multiple man-hours for data extraction and transcription, which may lead to errors.[228, 229] An online tool may improve data collection and analysis, may improve the ease of study monitoring of trial procedures, and is becoming the standard of practice for RCTs, particularly those across more than one setting.[230] Conducting a fully online trial is not recommended, however,[231] and any online tool should be used only as an adjunct in the conduct of the trial.

In the pilot study, data on dressing changes and resources used was difficult to collect, particularly after discharge. In other studies, patients are often asked to complete forms related to resource use, such as patient diaries, that improve the ability to collect such data.[232] This data, along with that collected by researchers, forms an integral part of any cost-effectiveness analysis. For a trial which examines the cost-effectiveness of DACC-coated dressings for the primary prevention of SSI, it may be beneficial to improve data collection using a checklist such as the one suggested by Ridyard *et al.*[232] Important points to consider include prior consideration of which costs to measure, consideration of the methods used to collect data (such as patient diaries), consideration of the completeness of routinely collected data, collection of baseline data, and involvement of health economists in the planning and analysis phases.

In summary, moving to an online data collection and storage model, with improved methods for collection of data amenable to cost-effectiveness analysis, should be pursued as a result of the observations of this pilot study, as it has the potential to improve data collection and ultimately study validity. Electronic methods for monitoring treatment compliance have better outcomes that other methods, and electronic diaries show superior compliance when compared to paper diaries.[233, 234] For these reasons, incorporation of an electronic patient diary in any online trial management system should be considered.

4.5.1.6 The measured effect size, in order to inform the power calculation for a full scale RCT

The effect size seen in this pilot study was a reduction in SSI at 30 days from 25.71% to 16.22%, an ARR of 9.49% and an RRR of 36.9%.

In a two-arm randomised controlled trial, in order to detect a statistically significant reduction in SSI from 26% to 16%, at 90% power and 5% significance, 386 participants would be required in each arm. This would be a total of 772 participants, not accounting for any attrition (Calculated using *OpenEpi,* Open Source Epidemiologic Statistics for Public Health[235]). A total sample size of 925 would allow for a conservative attrition rate of 19.8%. At the median recruitment rate of 10 participants per centre per month, completing study recruitment in 18 months would require approximately 5 centres to take part in the trial.

4.5.2 The Clinical Effectiveness of DACC-coated Dressings vs Standard Care in the Primary Prevention of SSI

This study aimed, in part, to evaluate the efficacy of DACC-coated dressings as primary prevention for SSI following vascular surgery. To date, this is the only randomised trial of this intervention in this cohort, and one of only two randomised trials examining hydrophobic dressings for the prevention of SSI.[165] The results of this study indicate an effect of DACC-coated dressings to reduce the rate of SSI, although these findings did not reach statistical significance. In order to draw full conclusions, it would be necessary to increase the scale of any randomised trial to include sufficient patients.

4.5.2.1 Surgical site infection within 30 days of surgery

This study has shown a reduction of SSI from 26% to 16% when DACC-coated dressings are used as a primary preventative measure. This RRR of 37% is roughly half that of the single previous RCT examining hydrophobic dressings,[165] although the overall infection rate in our study was much higher. This is likely due to the significantly higher number of multimorbid patients, with an increased age, and a high prevalence of known risk factors such as smoking, PVD and diabetes. From our results, 11 patients would need treating with DACC coated dressings to prevent one

SSI (NNT = 10.5). The estimated cost per vascular SSI is reported as at least £3545, rising to £6103 in SSI following limb amputation.[80] The maximal additional cost of using a DACC coated dressing is around £13 per patient treated (albeit in a different patient cohort).[236] According to this NNT and dressing cost, a investment of £136 could prevent an SSI costing at least £3545. Further research is needed to fully assess the cost effectiveness of this intervention but these early results would suggest a potential for significant savings.

ASEPSIS scores at 30 days tended to be lower in the DACC-coated group (median [IQR] 0 [10] vs 3 [12] in the control group). Although this again was not statistically significant, lower SSI rates and lower average ASEPSIS scores suggest that DACC coated dressings may improve wound healing and reduce the risk of SSI over the course of 30 days.

When using ASEPSIS alone to assess for SSI, there was an 8.75% ARR, which equates to a 42.7% RRR. The ASEPSIS method, however, has a tendency to underreport SSI,[115] and is best suited to wound assessments in hospital,[117] which means SSI rates reported using ASEPSIS alone may not be representative of the true infection rate.

Because the CDC definition includes diagnosis of infection by an attending physician as a criterion for SSI,[73, 74] instances where patients were prescribed antibiotics for wound complications by the GP were treated as having experienced SSI for the purposes of primary outcome analysis. Patients with wounds have been shown to receive more antibiotic prescriptions in primary care than the general population,[237] potentially because of a diminished perception of the risk associated with overuse of antibiotic agents.[238, 239] Antibiotics may also be prescribed without the patient being reviewed in person, instead arising as a result of a telephone consultation, a practice that is increasing in frequency.[240] The difference in rates of SSI in our study between the ASEPSIS and CDC definitions of SSI may arise as a result of this imbalance of antibiotic prescription in the community.

The overall infection rate in the study population (20.8%) is higher than other studies examining SSI in vascular surgery.[78, 86, 108] As with other studies, this is likely because SSI is generally underreported, and post-discharge surveillance is poor.[83, 222] Within

the confines of a research study, to ensure accurate and consistent diagnosis would require an in person research team review of all index wounds whenever any concern for SSI was raised, a system which may be infeasible. Within the conduct of a study such an intensive regime for follow-up may be required to maintain the internal validity of the results but may adversely affect the external validity as this would be practice that did not mirror real-world practices. However, a pragmatic trial design for an upscaled trial which simply records GP attendance and use of oral antibiotics as resource use associated with the intervention arm would be more important as a predictor of cost efficacy following introduction into current NHS services.

4.5.2.2 Factors that may increase the risk of developing SSI

We independently examined factors on a patient and procedural level that may increase the risk of developing SSI, then used this analysis to conduct a logistic regression analysis to examine the effects of these factors in cases of SSI. In our study, diabetics and those with PVD were found to be more likely to experience SSI. The links between diabetes, PVD and SSI are well known,[63, 95, 105] including poor tissue oxygenation, decreased growth factor production and delivery, reduced macrophage function, and increased levels of reactive oxygen species.[56, 63, 64] Those treated with DACC after major limb amputation or lower limb arterial surgery (both sequelae of PVD) showed an absolute reduction of infection of 9.48% and 5.36% respectively. Diabetics treated with DACC showed an ARR of 4.8% (RRR 13.8%) when compared with control. Those who were current, or ex-smokers, showed an 11.1% ARR in SSI when treated with DACC coated dressings (50.9% RRR) compared with the control dressing.

We used a logistic regression analysis to identify the effect of dressing choice on SSI in a model including other risk factors for SSI shown in our data. 10 variables were included in the model, including randomisation group.[170] The analysis showed that, in this group of patients, rates of SSI were more likely impacted by sex, BMI, surgical procedure, smoking status and surgical drain placement than the choice of dressing. This is not entirely unexpected, given that the study was underpowered to show such an effect due to its design as a feasibility phase study. However, the analysis does identify those individuals at risk of SSI, and using this to target the use of DACC coated

dressings in order to provide the maximal protective effect may be of benefit for future studies.

The observation that those in which a drain was placed is of interest. The numbers of participants in which a drain was placed was very small (7 and 5 in the intervention and control groups respectively), which may skew the data. However, there are two possible further explanations. Firstly, there is the possibility that a drain acts as a conduit for bacterial ingress into the wound, and, as the drain exit is often away from the index wound and therefore not covered by the intervention dressing, the effect of the dressing is not seen. There is also the possibility that drains are more commonly placed in high risk wounds, where the surgeon is expecting a possible exudate, collection or haematoma, which are all vectors for SSI. These wounds may be at an intrinsically higher risk of SSI which may be reflected in the results observed in this study.

There were unexpected observations within this analysis. Firstly, there was no significant difference between males and females with regards to SSI (Although the difference, 80% male vs 61% female, was approaching statistical significance, p = 0.057). In other trials examining SSI results have shown a trend towards more males developing infection.[241] This may suggest that males are at a higher risk of SSI, or could just reflect the fact that more men undergo vascular surgical procedures.[88]

4.5.2.3 Reduction of SSI in procedures involving an implant

SSI in an area containing a prosthetic implant may have disastrous consequences for the patient, including limb loss and death,[94, 242-244] and may be associated with a significant cost for healthcare providers.[245] In our study, there was a reduction of SSI from 24% to 7.7% when DACC dressings were used, although this was not statistically significant. All of the incidents of SSI in this cohort occurred before POD 30, with no further infections seen between POD 30 and POD 90. Given the consequences and costs of SSI in this patient cohort, the 67.9% RRR seen in this study may be practice-changing, and may represent a significant benefit to the patient.

4.5.2.4 Satisfactory healing

The ASEPSIS tool allows for the grading of wounds, with a classification of 'impaired wound healing' (IWH) between normal healing and SSI.[112, 169] More patients allocated to the DACC-coated dressing achieved satisfactory healing by 30 days than those in the control group, and fewer patients were classified as having IWH or SSI, although this was not statistically significant as again the data is underpowered to demonstrate this effect.

4.5.2.5 Consequences of infection

Patients who were allocated to the DACC dressing and experienced an SSI required fewer antibiotic prescriptions and spent fewer days in hospital. The importance of this cannot be understated, as the additional cost per extra day spent in hospital due to SSI is estimated as around £290.[80] Those in the DACC-coated group did have a higher readmission and reintervention rate, suggesting that the SSIs that they experienced may have been more severe, however there was no significance to these results. A surface dressing such as the intervention dressing in this study may have a smaller effect on more severe deep incisional or organ space infection, that are more likely to result in readmission and reintervention. It may also be simply that too few participants experienced these sequelae for there to be statistical significance. Survival to 30 days and 6 months was similar between groups. Mortality in our study was similar to that seen in other surveillance data,[246] although no patients in our cohort died as a direct result of an SSI.

4.5.2.6 Quality of Life

Establishing the impact of treatment upon QoL in this pilot trial was difficult due to the small number of participants, the poor response rate to QoL utility questionnaires, and the short follow-up period of the study. In general, patients in the DACC-coated group showed a greater change in QoL when compared to those in the control group, with significant improvements in the PF, RP, BP, SF, RE and HT domains of the SF-36 utility, in comparison to improvements only in the HT domain in the control group, across the study period.

When looking at the change in QoL between those experiencing SSI and those who did not, there is a statistically significant improvement in QoL across the study period in those who did not experience SSI, compared to those who did. This is in line with other evidence that SSI adversely affects QoL.[82] As shown in Figures 30 and 31 (PCS and MCS scores of the SF-36 utility), QoL decreased immediately post operatively, and increases in those without SSI, remaining poor in those who experience SSI. The EQ-VAS utility showed a general increase in QoL in those with no SSI, in comparison to a maintained/declining QoL in those with SSI (Figure 32).

It is plausible that the observed improvement in QoL in the DACC-coated group may be as a result of fewer incidents of SSI. QoL may be influenced by the severity of surgery performed (a factor that should be controlled for by the randomisation process) and by the clinical outcome of the surgery, as well as other, unrelated factors. For this reason, it may benefit any future study to utilise a disease-specific QoL tool, such as the Wound-QoL[247] or the Cardiff Wound Impact Schedule,[248] in addition to the General Health-Related QoL tools used in this study.

4.5.2.7 Time to return to work or normal activity

We compared the time to return to work or normal activity firstly between those randomised to the intervention group and those randomised to control, and subsequently between those who experienced SSI and those who did not.

In the first comparison, there was no statistically significant differences between groups. This may simply be due to the study being underpowered to detect such a difference. However, with a non-significant difference in total number of inpatient days, it stands to reason that the post-operative course of each group is similar, with similar periods of recovery and time before normal activities are resumed.

In the second comparison, a statistically significant difference was found in the time to return to normal activities between those who experienced SSI and those who did not. Given that patients with SSI have extended stays in hospital and often require further procedures,[80, 82, 249] it is not surprising that patients require a more prolonged period of recovery compared to those without infective complications. This may, in part, also explain some of the differences in QoL between these two groups shown

above; being unable to return to regular activities due to an SSI is likely to impact upon the QoL of the patient.

4.5.3 Limitations of This Study

As a free-standing RCT, this study has a number of limitations. Firstly, the study did not recruit enough participants for results to reach statistical significance. This was however a planned outcome, due to the nature of the study as a pilot feasibility model. Further trials with adequate recruits are needed to make firm conclusions about the effect of DACC coated dressings on rates of SSI.

Secondly, there was a high rate of drop out within the trial, with 30 patients in total (almost 21%) who either died, withdrew, or were lost to follow up. This high attrition rate impacts the validity of the study, and reinforces the need for altered study protocols in future trials to avoid such high attrition.

Finally, this trial was an observer blinded trial, in that patients and those applying trial treatments were not blinded to dressing allocation. In order to limit the effect of this bias, wound assessors were kept blind to the dressing allocation, a strategy employed in a number of different studies evaluating dressings.[165, 225, 250] This level of blinding may mitigate some, but not all, bias introduced by having an open-label trial.

4.6 Conclusions

As a pilot feasibility study, this study has shown that a large scale RCT with close to a thousand participants should be achievable, with some amendments in the follow-up protocol in order to reduce the burden to patients and improve the levels of return. Patients are eligible and willing to be recruited, and both dressings used in this study are tolerable and showed no adverse reactions. Furthermore, with an estimated relative risk reduction of over 35%, in addition to the growing body of evidence to support the use of DACC-coated dressings in preventing SSI, a significant study is needed to show the true effect of this promising intervention, including its cost effectiveness, in order to influence current clinical practice.

CHAPTER 5: DISCUSSION

5.1 Overview

The aim of this thesis was to provide a body of work to examine the feasibility of conducting a large scale, multi-centred RCT examining the use of DACC coated dressings in the primary prevention of SSI in vascular surgery. This intervention is all but untested with the exception of a single RCT which was at significant risk of bias, and in a markedly different cohort of patients from our own.[165] The landscape of studies investigating dressings for the primary prevention of SSI is one of no firm conclusions and trials that are flawed in their methodology.[134]

Study one laid the foundations for the work, outlining the paucity of evidence regarding the use of DACC-coated dressings in the prevention of SSI. Multiple studies into the use of DACC-coated dressings in chronic wounds exist, though these are largely product evaluations or case series, in a number of instances directly funded and/or published by product manufacturers. Importantly, no instances of reaction or resistance to date have been reported across the spectrum of use, which suggests an intervention that is tolerable and safe. The overall findings were that DACC coated dressings were useful in treating infection already present and, in one case, reduced the risk of developing infection in the primarily closed wound. The findings from study one outlined the need for further investigations into this technology, in a cohort of patients at an intrinsically high risk of SSI.[94, 108]

Study two was used as a proof-of-concept study to identify any potential benefit of DACC-coated dressings in patients undergoing vascular surgery. We limited outcome measurement to the presence or absence of SSI, recruiting 200 patients to the study. Recruits were representative of the wider vascular surgery population, with a high number of smokers and diabetics.[251] The study found an absolute reduction in SSI rates of 9%, and an RRR of 47%, suggesting a potentially significant clinical benefit to be derived from its use in this cohort of patients.

In study three, we explored the feasibility of conducting an RCT investigating DACC-coated dressings in preventing SSI. Pilot studies are increasingly common and

valuable when conducting trials that may be complex, large scale or across a number of localities.[178, 179, 252] Using the effect size seen in study two, it was estimated that over 700 recruits would be needed for a randomised study; such an undertaking could be fraught with difficulty without an adequate pilot phase. Study three provided both clinical and feasibility data to support the conduct of such a trial, and showed that the clinical reduction in SSI rates, namely a 37% RRR, warrants further investigation with an adequately powered RCT.

DACC coated dressings appear to have a sizeable effect on rates of SSI in a cohort of patients who, due to a number of factors, may be at risk from the point at which they undergo surgery. The work contained within this thesis should allow for the conduct of a robust clinical study to properly evaluate their clinical and cost effectiveness.

5.2 Main Findings

5.2.1 The Existing Evidence for the use of DACC-Coated Dressings as Primary Prevention for SSI

In study one, we conducted a systematic review of evidence examining DACC-coated wound coverings. Systematic reviews provide the highest level of evidence in interventional studies[253] and authors may often calculate a combined effect size of a number of different studies.[254] In our systematic review, we found a paucity of evidence for the use of DACC coated dressings in any setting, despite a thorough search strategy of a number of databases. 17 studies overall were included in the review, and the results were divided into two categories; DACC-coated dressings in chronic wounds and DACC-coated dressings as primary prevention for SSI. The latter category became the focus of this thesis. Two randomised trials[159, 165] investigated the use of DACC coated dressings as primary prevention for infection. The two studies were heterogeneous, and so synthesis of the results was not possible. Both trials were at risk of bias, due to a lack of true randomisation and blinding. Only a single trial[165] showed results that were statistically significant, though again this study was flawed in its methodology. In summary, the use of DACC-coated dressings for the primary prevention of SSI showed promise, however the available evidence was not sufficient to prompt a widespread change in clinical practice.

5.2.2 The Potential Effect on SSI Rates When Using DACC-Coated Dressings Post-Operatively

Studies two and three contained evidence to suggest that DACC-coated dressings, when used post-operatively, reduce the risk of SSI in vascular surgical wounds. As surgeons take on increasingly complex vascular interventions in a population that is ageing and comorbid, rates of SSI are likely to climb. In parallel, antimicrobial resistance is growing, and close to becoming a crisis on a multinational level.[255] Study one identified the potential beneficial effect of DACC-coated dressings in reducing SSI, and in studies two and three we began to quantify this potential benefit.

In study two, a reduction of SSI was seen from 19% to 10% when DACC-coated dressings were used, with a significant reduction in infection seen (10% to 1%) within the first 7 days. Given the nature of DACC, the timing of this maximal effect may be logical, if the ingress of bacteria into freshly incised wounds is prevented by hydrophobic binding to the dressing. The effect size observed over the 30 days follow-up period was in keeping with observations of other interventions to reduce SSI in vascular surgery, undertaken in the same centre.[241] However, given the methodological limitations of study two, it was felt essential to investigate this positive effect thoroughly through a properly conducted randomised trial, leading to study three.

A two-armed RCT demonstrating the same effect as study two would require over 700 participants to be adequately powered. Such an undertaking would be large, complex and ultimately costly, with RCTs often running into hundreds of thousands of pounds to conduct.[256] Study three, therefore, was primarily conducted to examine the feasibility of such a trial. However, 144 patients were still recruited, randomised, and received either the trial intervention or control. Although not statistically significant, a reduction of SSI at 30 days from 25.7% to 16.2% was seen. This effect size represents an OR of 0.56, similar to large trials examining SSI in other surgical disciplines.[257, 258] The effect size was lower than the only other RCT examining DACC-coated dressings in the prevention of SSI, however the overall infection rate seen in that study was much lower than in ours.[165] Interestingly, there was little to suggest the significant benefit in the early post-operative stages as seen in study two, instead

the maximal effect was seen between days 7 and 30. It is well known that wound healing is impaired by the presence of diabetes, increased BMI and PVD,[56, 64, 259] findings that were reflected in our study population.

One interesting effect noted between studies two and three, is the apparent point of maximal effect of using DACC coated dressings as prophylaxis against SSI. In study two, the maximal protective effect appeared to be in the early post-operative period, with a statistically significant reduction in SSI after 7 days. This is in stark contrast to the effects seen in study three, in which the ASEPSIS scores after 7 days were actually higher in the intervention group than in the control, with this being trend being reversed at 30 days. One possible explanation of this effect is that the initial dressing application was in theatre, on a theoretically sterile wound. Any ingress of bacteria would then occur only after the dressings were changed on at least day 2 and then subsequently following that; the DACC coated dressings should bind and render inert these bacteria in the intervention group, whereas multiple dressing changes in the control group allow for a steadily increasing bacterial load throughout the 30-day period, leading to a protective effect in the intervention group that continues past the 7-day point. Bacterial load has been shown to increase in wounds during the post-operative period despite other factors such as systemic antibiotic therapy,[260] and bacterial load in the wound is correlated with rates of wound complications,[261] so an intervention specifically targeting bacteria at the wound site could prove significant. In study three the observed differences were not statistically significant, and no patients had experienced SSI by 7 POD – it is also plausible that the study was simply underpowered to observe such an effect.

5.2.3 The Feasibility of Conducting a Large Scale Randomised Controlled Trial to Investigate the Use of DACC-Coated Dressings Post-Operatively

Study one identified a need for high quality research into DACC-coated dressings, and studies two and three showed evidence of a sizeable benefit to their use as a primary preventative measure against SSI. Study three was used primarily to investigate the

feasibility of conducting a randomised study which would be robust and informative, eliminating the bias seen in other trials investigating DACC-coated dressings.

Eligibility was high at over 70%, in line with eligibility seen in other clinical trials.[262] Around 60% of those that were eligible went on to randomisation, with unacceptable follow-up arrangements being cited by the majority of those eligible but not randomised. Recruitment occurred at a rate of around 10 patients per month, much better than quoted recruitment rates in other studies.[189]

Participants found the study dressings acceptable and fit for purpose in the majority of cases, though for some wounds the dressings were unsuitable. This is to be expected given the complexity of wound management systems for wounds that have broken down or experienced complications. There were no recorded instances of allergy to the DACC component of the intervention dressing, or any suggestion of safety concerns that may halt the process of a larger study.

In their current form, the methods used for wound assessment and follow up for the trial are unsuitable for use in the conduct of a larger study. The ASEPSIS scoring tool showed a disparity in diagnosing infection when compared with the CDC definition of SSI, an observation that corresponds with other investigations into these tools.[115] Our pilot study was also hampered by a higher-than-expected attrition rate, which, if replicated in a larger trial, may lead to inaccurate results.[263]

The work in this thesis should allow for the conduct of a robust clinical trial investigating the use of DACC-coated dressings to reduce SSI, something which we would suggest has real merit given the scale of the potential benefits.

5.3 Validity and Applicability

5.3.1 Study Populations

Studies two and three of this thesis were a cohort study and pilot RCT undertaken in a university teaching hospital with a tertiary referral service for vascular surgery, that serves approximately 1.2 million people within the areas of Hull, East Yorkshire and Northern Lincolnshire.[168] Both studies recruited patients that closely represented the

wider population within vascular surgery. Recruits were largely male, with an average age of around 63 years. Rates of smoking, diabetes, obesity and PVD were high. These are similar observations to those in other large, randomised trials within vascular surgery.[264, 265]

Male sex, advancing age, smoking, PVD and diabetes are all recognised risk factors for wound complications such as breakdown or infection.[56, 98, 108] Inclusion of a high number of participants with one or more of these comorbidities allows the results shown to be applied to the wider population of patients within vascular surgery without fear of misrepresentation.

Of note is the ethnicity of participants – all participants in study two and all with the exception of two patients in study three were White European in origin. Whilst this may be reflective of the local population where the study was conducted, in the United States of America those whose ethnic origin is Black or Hispanic are at a higher risk of wound complications,[266] though this may be related to the wider socioeconomic picture as opposed to an issue purely relating to race. Nonetheless, the limited diversity of ethnicity of study participants should be noted as a relative limitation of the study.

5.3.2 Eliminating Bias Within the Studies

Throughout study two and study three, blinding was limited due to the nature of the intervention in question – the intervention dressing has a green coloured coating which makes it easy to identify (figure 25).

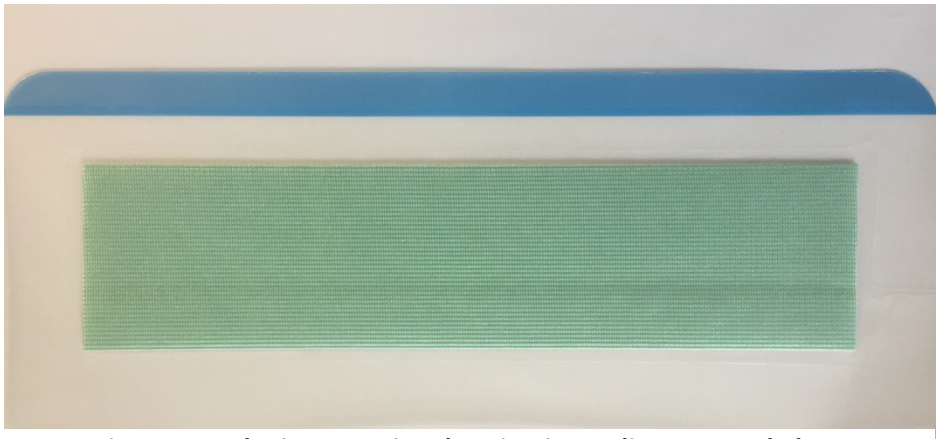


Figure 25 - The intervention dressing in Studies Two and Three

The coloured contact layer is easily identifiable.

Wound care trials are often limited by a lack of blinding,[267] due to complexities surrounding wound coverings (for example, NPWT leaves a recognisable imprint on a wound[268]). Subjective outcome measures such as wound healing are open to overestimation towards the intervention arm when assessors are not blinded to treatment allocation.[269] In both studies two and three, an objective outcome measure, the ASEPSIS tool, was used to eliminate bias in the assessment of wounds. In study three, dressings were disposed of in opaque bags and wound assessments were carried out by individuals blinded to dressing allocation, and participants were encouraged not to reveal their dressing allocation to assessors throughout their study visits. During the set-up phase of this study the author of this thesis approached the manufacturers of the dressing to enquire about a placebo dressing; unfortunately, this was technically infeasible as the cost of pursuing regulatory approval as well as commercial and manufacturing costs made it non-viable. Other objective outcome measures, such as patient reported QoL and mortality, were also used.

Study three was hampered by a high attrition rate, which risks introducing attrition bias into the findings.[263] However, rates of attrition were similar between randomisation groups, which should limit any potential effects.

5.3.3 Applicability of the Intervention

The intervention in question in this thesis is available on the open market, and is available via the NHS supply chain, the stockists for NHS hospitals in the UK. It is, as used in this thesis, directly interchangeable with simple dressings when used to cover primarily closed wounds. Although not suitable for complex, highly exuding wounds, hydrophobic, bacteria-binding technology is available within other dressing materials such as gauze and ribbon packing, which may be used on such wounds, although the evidence for their use is similarly limited to date.

5.4 Limitations

The limitations of the research contained within this thesis must be recognised. Studies two and three share some limitations, though all three studies have their own, unique limitations to be acknowledged.

Study one was a systematic review of the existing evidence for the use of DACC-coated dressings in wound infections. The review was limited to published research in peer-reviewed journals, excluding case studies with less than three participants. It is possible that research presented at conferences, small case studies in non-peer reviewed journals, and research undertaken but not published, was missed from the review. However, any such research may be of low quality or impact, and therefore at significant risk of bias. There was, in general, a lack of research investigating the use of DACC coated dressings, which led directly to the research conducted in Studies Two and Three.

In study two, a non-randomised study was undertaken. This is a limitation as randomisation within a study aims to limit bias by ensuring no systematic differences exist between intervention groups, known or unknown, that may affect outcome.[176] However, when compared, participants within each group were well matched, suggesting that the effect seen was less likely due to a disparity between individuals allocated to each intervention. Furthermore, the study was only ever intended as preparatory work for a potential randomised, two-arm intervention study, such as that conducted in study three.

As previously discussed, studies two and three were unblinded, or open-label studies. The limitations of a lack of blinding must be taken into account when interpreting the outcomes seen in each study, however every effort was made in study three to limit any bias introduced by making use of blinded assessors, a strategy which has been shown to be superior to the use of non-blinded assessors.[270] As previously mentioned, regulatory and financial limitations prevent the production and use of a placebo dressing from the same manufacturer which would otherwise be the gold-standard comparator in a trial such as this.

Study three was intended as a pilot feasibility study to inform the design of a larger RCT. As a standalone trial, it has several limitations. As a single-centre trial, there are questions about the external validity of the findings, both feasibility and clinical. However, the findings will allow for the amendment of trial protocols to account for difficulties encountered, which should improve the conduct of a larger trial. Furthermore, every effort has been made to present every detail of the trial conduct, participants, outcomes and difficulties encountered.

A major concern was the high attrition rate seen within the study. This calls into question the acceptability of the study methods employed, and the suitability of the patients recruited. This would need to be addressed within the protocol of any subsequent studies, and every effort made to reduce the participants lost within the study period.

Pilot studies are intended to examine the feasibility of conducting a large trial and may be able to predict the relative success of said study. For this reason, the results of the efficacy study should be taken with caution.[252] With this in mind, investigators can be cautiously optimistic about the effect size seen in study three, but any subsequent studies should incorporate the results of each study of this thesis in their design.

In particular, study three identified several groups of patients which may benefit from a targeted intervention to reduce SSI. Firstly, in patients undergoing surgery involving a vascular prosthesis, infection rates were reduced from 24% to 7% through the use of the intervention dressing. Given the consequences and costs of SSI in this patient cohort, the 67.9% RRR seen in this study may be practice-changing and may represent a significant benefit to the patient. Further investigation within this sub-population is therefore strongly recommended.

Furthermore, further analyses of those patients experiencing SSI identified BMI, smoking status and drain placement as risk factors for the development of SSI. Using this to target the use of DACC coated dressings in order to provide the maximal protective effect may be of benefit for future studies.

Conversely, the results of study three may allow future studies to exclude particular cohorts of patients. In study three, those undergoing CEA were excluded due to a significantly lower SSI rate than other vascular surgical procedures.[90] In the study, those undergoing open abdominal aortic surgery had very low SSI rates, and may also be considered for exclusion. In addition, it was identified that patients undergoing surgery for dialysis access had high attrition rates but low infection rates, and future studies may benefit from their exclusion.

Finally, as the studies contained within this thesis were aimed at providing useful pilot data for further research, no healthcare financial data has been collected. In current practice, incorporation of cost-effectiveness into clinical studies is essential in order to effect meaningful change to practice. For that reason, any subsequent studies should aim to investigate the cost-effectiveness of the intervention in question.

5.5 Avenues for Further Research

The findings of this thesis could lead directly to the conduct of a multi-centred RCT with close to a thousand participants, investigating the clinical and cost-effectiveness of DACC coated dressings for the primary prevention of SSI in vascular surgery in comparison to a simple dressing control. In addition, this work could be expanded to encompass other surgical specialties in which SSI is either prevalent, or where the consequences of SSI may be disastrous, such as cardiothoracic surgery, colorectal surgery, or plastic surgery.

Within study three, we identified factors inherent in both the patient and the operative conditions that may increase the risk of SSI through the use of binomial logistic regression. There may be a rationale to limiting the focus of any investigation to 'at risk' groups, such as those with diabetes, smokers, high BMI, or a combination of factors, to identify the most cost-effective means of distributing this dressing. This could be in combination with examining other novel wound coverings, such as topical single-use NPWT, or active dressings such as honey, PHMB or silver coated dressings.

Further research may come in the form of laboratory studies, examining the use of hydrophobic dressings in multi-drug-resistant organisms. Lab evidence exists to suggest the efficacy of hydrophobic dressings against MRSA,[143] however a real-world clinical evaluation of such dressings against this and other resistant organisms such as *Acinetobacter*[271] and *Enterococci*[272] would be welcomed, particularly in this age of growing antimicrobial stewardship. A combination study, where dressings are applied in clinical practice and then analysed in the laboratory for levels and species of adherent bacteria, may evaluate the mechanism of action and improve the way the dressings are used clinically. Finally, the use of hydrophobic contact layers may be incorporated into studies examining wound healing by secondary intention, as a direct comparison for other wound coverings such as NPWT.[273]

Developing the feasibility aspect of this thesis could be a novel avenue of research that may improve the conduct of wound care trials across the board. Trials in wound care that are high level and well conducted are rare,[124, 268, 274] often because of a high loss to follow-up, heterogeneity of wounds, and poorly defined endpoints.[267, 275, 276] The work in this thesis could lead to the development of new strategies to improve the monitoring of wounds, improve clinical follow-up within research trials, and ultimately improve the quality of RCTs in wound care and wound healing. Addressing barriers to follow-up may not only improve retention within clinical trials examining wounds and wound care but may improve access to healthcare in areas where patients find it difficult to access clinical time.

CHAPTER 6: CONCLUSIONS

SSI is the second most common healthcare acquired infection and is a significant cause of mortality and morbidity to patients. In an age of antimicrobial stewardship, strategies to improve the prevention of SSI, particularly those which limit the effect of bacterial resistance, should be explored by the wider scientific community. The work in this thesis has led to the following conclusions:

1. The available evidence suggests that DACC-coated dressings show promise in the treatment of wound infection, and in the primary prevention of SSI in incisional wounds.
2. The use of DACC-coated dressings in patients undergoing vascular surgery may reduce the incidence of SSI.
3. Conducting a large-scale randomised trial in order to identify the true effect of such dressings is not only feasible, it is justifiable given the risk reduction seen in these studies.
4. In order to conduct such a trial, effective strategies for the follow-up of patients in order to identify cases of SSI must be explored.
5. Further research is required to establish the clinical and cost-effectiveness of DACC-coated dressings in the prevention of SSI in primarily closed incisional wounds.

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CHAPTER 8: APPENDICES

8.1 List of Appendices

Appendix 1 – Summary of Included Studies

Appendix 2 – Patient Information Sheet

Appendix 3 – Participant Consent Form

Appendix 4 – Ethical Approval Document

Appendix 5 – PHE Post Discharge Questionnaire

8.1.1 Appendix 1 – Summary of Included Studies, Study One

Table 38 – Summary of included studies: A Systematic Review of the Use of Dialkylcarbomoylchloride- Coated Dressings in the Management and Prevention of Wound Infection

REFERENCE	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES	PRIMARY FINDINGS
STANIROWSKI 2016[165]	Single blinded, randomised control trial	543 Females >18 undergoing planned or emergency caesarean section	Randomised to either DACC coated post-operative dressing or standard surgical dressing	Superficial or deep SSI within the first 14 days after CS (defined as per CDC)	SSI rates of 1.8% in DACC vs 5.2% in control (p=0.04)
STANIROWSKI 2014[166]	Single blinded, randomised, controlled pilot study	142 Females >18 years undergoing planned or emergency caesarean section	Randomised to either DACC coated post-operative dressing or standard surgical dressing	Superficial or deep SSI within the first 14 days after CS (defined as per CDC)	SSI rates of 2.8% in DACC vs 9.8% in control (p=0.08)
CHOI 2015[152]	Case series	7 patients (4 male) requiring skin graft of varying thickness on clean surgical wounds	Skin graft dressed with DACC coated dressing and tie-over dressing for 5 days	Wounds checked for infection at 5 days, 14 days and	No wounds experienced infection

				30 days post-procedure	
BULLOUGH 2012[151]	Case series	4 patients with complex open abdominal wounds	DACC coated dressings and swabs used as a wound contact layer for the duration of treatment	Wound infection recurrence; wound dimension; wound healing; pain during dressing changes; exudate and odour	3 of 4 wounds healed, and all signs of wound infection had resolved by day 14 of treatment.
GENTILI 2012[154]	Non-comparative, double blind, pilot study	19 consecutive patients with chronic lower limb ulcers	Wounds were treated with a 0.9% NaCl saline solution rinse, surgical debridement and application of DACC dressing. The study was performed during a 4-week period.	Evaluation of wound condition, quality of life, bacterial load	66% of wounds reduced in size. Reduction of bacterial load in all cases.

PIRIE 2009[161]	Case series	3 patients (one male) with chronic non-healing wounds referred to tissue viability services	DACC coated dressing used as a primary wound contact layer in combination with other dressings and therapies	Wound healing, evidence of infection, wound size, exudate levels	All showed clinical improvement (reduced wound size and slough).
KAMMERLANDER 2008[157]	Non-randomised multi-centre evaluation	116 patients (62 male) presenting to one of four European hospitals with a wound deemed to be at high risk of infection	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime	study questioned whether it could reduce inflammation; reduce infection; improve wound healing; be patient tolerable	81% of wounds were successfully treated for infection. 21% of wounds healed completely.
HAMPTON 2007[155]	Case Series	21 patients (7 male) with non-healing (>3 months) wounds that	Patients were treated with Cutimed® Sorbact® as part of	Inflammation, exudate, malodour, wound size, pain	60% of wounds healed, 100% had reduced exudate levels and 58% had

		were not clinically infected	their therapeutic regime		reduced wound odour
MOSTI 2015[160]	Randomised, comparative, single centre study	40 patients >18 with critically colonised or locally infected vascular ulcers of duration ≥6 months	Patients randomised to Silver containing hydrofibre dressing or DACC-coated dressing	Primary: Ulcer bacterial load	Reduction of bacterial load of 73.1% DACC vs 41.6% Silver (P<0000.1)
SKINNER 2010[164]	Case Series	4 patients (3 male) with diabetic foot ulcers	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime	Bacterial colonisation, infection, wound healing	One wound healed completely. ¾ progressed towards healing.
POWELL 2009[162]	Case series	6 patients (3 male) with a variety of wounds showing clinical infection or delayed healing	Cutimed® Sorbact® used as a wound contact layer for 2-8 weeks	Inflammation, exudate, odour, wound healing	100% of wounds were reduced in size, exudate and odour. 80% wounds healed completely

MEBERG 1990[159]	Randomised control trial	2441 newborn infants	Patients alternately allocated to umbilical cord stump dressing with either (i) DACC coated dressing or (ii) daily cleansing with 0.5% chlorhexidine in 70% alcohol	Infection in the newborn (conjunctivitis, pyoderma, paronychia and omphalitis)	No significant difference in either to overall rate of infection or in omphalitis
BRUCE 2012[150]	Multi-centre evaluation	13 patients (7 male) with chronic wounds of varying aetiology with signs of infection	Treated with DACC-coated dressings for 28 days or until signs of infection had resolved	Erythema, pain, heat, oedema, odour, exudate	86% reduction in infection; reduction in wound size in 79% of wounds
DERBYSHIRE 2010[153]	Case Series	3 patients with wounds of duration > 4 years.	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime.	Wound size, wound healing, resource use, pain, exudate levels	All wounds were cleaner, dryer, and required less nursing care/dressing changes

KLEINTJES 2015[158]	Prospective pilot study	13 patients >16 years of age with burn wounds large enough to accommodate three different trial dressings	Burns were dressed with DACC coated dressings, Acticoat® and Silverlon®, three dressings to the same burn	Wound swab MC&S, visual inspection of wounds	Wound areas dressed with DACC-coated dressings appeared subjectively cleaner and has less bacterial growth on MC&S
SIBBALD 2012[163]	Case Series	14 patients with lower limb ulceration (8 diabetic foot ulcers, 6 venous leg ulcers)	Ulcers dressed 3 times a week for 4 weeks with a DACC-coated dressing	Superficial infection (as assessed by NERDS or STONEES criteria), total ulcer surface area, pain	Reduction in total average surface area from 1.74cm^2 to 1.15cm^2 (p=0.337). No significant difference in superficial or deep infection rate.

HAYCOCKS 2011[156]	Case Series	19 patients (13 male) with diabetic foot ulceration up to the age of 80 years, with a total of 29 separate wounds studied	All wounds treated with a DACC-coated dressing as a wound contact layer for 4 weeks	Infection, healing, patient and clinician assessment	By study end, all 29 wounds had reduced signs of infection. 69% of wounds had reduced in size and 27.6% of wounds had healed.

8.1.2 Appendix 2 – Patient Information Sheet

DACC in the REduction of Surgical Site INfection – The DRESSINg Trial

Patient information sheet

Part 1

Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Your consultant believes you may be a suitable/ willing participant for a research study being carried out in Hull. The study is being carried out by a research doctor attached to the Department of Vascular Surgery, undertaking a research degree at Hull University.

You are being asked to take part in this study because you need an operation which is considered to be a 'clean' vascular operation.

Surgical infections

Wound infections can increase the amount of time you spend in hospital and may result in you having to visit your GP for antibiotics. It is also possible that it may delay your return to work or normal activities. It is therefore important for us to look at ways that we can reduce how often wound infections occur.

You have been invited to take part in a clinical trial to see if using different wound dressings after an operation has an effect on how often wound infections occur.

Specifically, we are comparing two different dressings. Both dressings are used routinely in clinical practice, but one dressing has a coating (DACC), that traps bacteria, makes them inactive, and removes them from the wound when the dressing is changed. We would like to study whether this additional coating improves infection rates in people who have had surgery.

To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss the study or ask any questions.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to participate you will be given this information sheet to keep and be asked to sign a Consent form. You are still free to withdraw at any time and without giving a reason. Your non-participation or dropping out of the study will not affect your planned treatment and care in any way.

Before you can begin the study

You may read the full study protocol as well as this Patient Information Sheet, which gives you many details about the study. The recruiting Investigator will tell you about any potential adverse events that could occur in this study. You will be told exactly what the study entails and what will be required of you. You are encouraged to ask questions of the Investigators conducting the recruitment interview until you are satisfied that you fully understand the nature of the study and the requirements.

What happens in the study?

If you think you might be interested in taking part in the study, you will have a short interview with one of the researchers so we can collect some details from you and make sure there is no reason not to include you in the trial. Once you are enrolled in the trial we will ask you to complete two short questionnaires. One questionnaire will ask you questions about how we, as a study team, can best keep in touch with you, and keep up to date with the status of your wound.

Your operation will proceed as normal but at the end of the surgery, rather than your surgeon deciding which dressing to use this will be randomly assigned. This means that a computer program will be used to allocate you to one of two different

dressings, similar to flipping a coin. Your odds of receiving one dressing or another are equal, and a computer 'flips the coin' in order to remove any possibility of bias.

After your procedure you will be sent short questionnaires to fill in 5 days after your operation, 30 days after your operation, 3 and 6 months after your operation. They will ask you to describe any problems you have had with your wound and how you are feeling in general. They will take no longer than half an hour to complete for the majority of people. These questionnaires will be sent by post, and we ask you to return them by post to the research office. Instructions for returning the questionnaires will be included when they are sent to you.

If, in your initial questionnaire you have said you would be happy to, shortly before your appointments at hospital the study team will ask you to take a photograph of your wound with your mobile phone, or the phone of a family member or friend, and send this to us on a secure NHS email address.

On around day 5 and day 30 after your operation, you will come in to the hospital and be seen by a nurse or doctor who will collect your questionnaires and ask you a few questions about how you have been. If you are still in the hospital the doctor or nurse will visit you on the ward. Your dressings will be removed and another nurse or doctor who does not know which dressing you have been using will look at your wound. Photographs of your wound will be taken to be looked at by a third nurse or doctor, to make sure we are assessing your wound fairly and that the trial is not biased towards one dressing or another.

Will the photographs be anonymous?

Yes. Our photographs will only be of your surgery wound and the skin around it. We ask that any photographs that you take of your own wound are also anonymous.

Are there any risks to participating in the study?

Taking part in the trial will not alter the operation or treatment that you will receive. The only difference is that instead of the surgeon deciding which dressing to apply at the end of the surgery, this will be randomly assigned.

Are there any benefits to taking part?

We hope that we may be able to reduce the number of wound infections in the future.

Are there any costs to me involved?

You will not receive any expenses for any extra visits you may have to undertake as part of the research, though we will try to ensure that any follow-up visits you have as part of the study take place at the same time as your routine appointments.

What happens when the research study stops?

When the study is complete, you will continue to be followed up by your team as usual.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

If you have a complaint, please contact the following in the first instance: Dr Joshua Totty

A contact number for complaints will be given.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:

If you require any further information please contact:

Dr Joshua Totty,

Clinical Research Fellow,

Academic Vascular Surgery Unit,

Vascular Laboratory,

Hull Royal Infirmary,

Hull. HU3 2JZ

Tel: 01482 674643

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

If you withdraw from the study we will need to use the data collected up to your withdrawal.

What if there is a problem?

If you have a concern about any aspect of this trial, you should first ask to speak to the researchers who will do their best to answer your questions. If you remain

unhappy and wish to complain, you can do this via the NHS Complaints Procedure. Details can be obtained from;

Head of Complaints, PALS, Hull Royal Infirmary.

Tel: 01482 675508

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Hull and East Yorkshire Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. In the highly unlikely event that you suffer from injury or illness as a result of participation in this study, indemnity will be provided by the Hull and East Yorkshire hospitals NHS Trust. Compensation will be by the usual NHS procedures.

Will my taking part in this study be kept confidential?

All the information obtained about you in the course of the study is confidential and will be kept in a secure locked room. The investigators performing the study and a study Monitor will have access to the data collected in this study. They may also be looked at by representatives of regulatory authorities and by authorised people from Hull Royal Infirmary to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

What will happen to the results of the research study?

The results of this study may be published or presented at meetings. You will not be identified in any report / publication or presentation. We would be happy to supply you with a copy of the results on request.

What will happen to my data at the end of the study?

Data will be stored securely for 5 years within the vascular surgical department in a locked area. There will be no information that can identify you individually stored.

Who is organising and funding the study?

This study is organised and funded through the Academic Vascular Surgery Unit, Hull Royal Infirmary.

Who has reviewed this study?

The ethics behind this study have been reviewed and supported by the National Research Ethics Committee.

Further information/independent advice

Independent advice regarding this study or any other aspect of your care can be obtained from the Patients Advisory Liaison Service (PALS) using the details below;

Patient Experience Service

1st Floor

Alderson House

Hull Royal Infirmary

Anlaby Road

Hull

HU3 2JZ

Tel. 01482 675508

Email: pals@hey.nhs.uk

What happens next?

Please discuss this information with your family, friends or GP if you wish. Any questions can be answered then or please do not hesitate to contact the research team on the number below. Thank you very much for taking the time to read this information sheet and considering taking part in our research.

Tel: 01482 674643

8.1.3 Appendix 3 – Informed Consent Form

PARTICIPANT CONSENT FORM

Consent to participate in:
A randomised controlled trial to assess the clinical and cost effectiveness of Dialkylcarbamoylchloride (DACC) coated post-operative dressings versus standard care in the prevention of Surgical Site Infection in clean or clean-contaminated, vascular or cardiothoracic surgery.

Chief Investigator: Mr George Smith (Senior Clinical Lecturer and Consultant in Vascular Surgery)
Co-Investigator: Dr Joshua Totty (Clinical Research Doctor in Vascular Surgery)

Patient initials:
Study number:

	Participants Initials
I confirm that I have been given adequate time to read and understand the patient information sheet version 4.0: 29/7/17. I have had the opportunity to ask any questions and have understood the responses.	
I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records	
I understand that participation in the trial is entirely voluntary and that I have the right to withdraw at any time without giving my reasons.	
I consent to my general practitioner and consultant surgeon being informed of my participation in the trial.	
I agree to take part in the trial	
I consent to photographic images of my wound being taken and stored by the research team for the purposes of the trial. I understand that these will be anonymous images with no information that will identify myself contained within them.	
I consent to have details stored by the research team and understand that my details will not be available to anyone other than the research staff or database administrator.	
I understand that the results of the study may be presented at medical conferences and published in medical literature in an anonymous form. No identifiable details will be released to anyone outside of the research team without my permission.	

To be included on consent form for other participating sites I agree that a copy of this consent form will be faxed/ emailed to Hull and East Yorkshire Hospitals NHS Trust	

_____	_____	_____
Name of Participant	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date

8.1.4 Appendix 4 – Ethical Approval Document

NHS
Health Research Authority
London - Harrow Research Ethics Committee
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 104 8049

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

25 November 2016

Mr George Smith
NIHR Clinical Lecturer/ST7 Vascular and General Surgery
Academic Vascular Surgery Department
Academic Vascular Surgery Department, Hull Royal Infirmary
Kingston Upon Hull
HU3 2JZ

Dear Mr Smith

Study title:	**A randomised controlled trial to assess the clinical and cost effectiveness of Dialkylcarbamoylchloride (DACC) coated post-operative dressings versus standard care in the prevention of Surgical Site Infection in clean or clean-contaminated, vascular surgery.**
REC reference:	**16/LO/2135**
IRAS project ID:	**215973**

The Proportionate Review Sub-committee of the London - Harrow Research Ethics Committee reviewed the above application on 23 November 2016.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Sadie McKeown-Keegan, nrescommittee.london-harrow@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

- **Social or scientific value; scientific design and conduct of the study**

The Sub Committee queried the status of the funding of this study and asked who would be providing the funding.

Dr Totty replied that at present the funding is provided by the Academic Vascular Surgery department at HYMS. He explained that he would be applying for a funding grant (RfPB or HTA) in order to take the trial multi-centred to achieve the sample size of 712 and that BSN Medical have agreed to supply the trial dressings at no cost.

The Sub Committee was content with the response given.

The Sub Committee asked how long Dr Totty's position of Research fellow was funded for at HYMS.

Dr Totty replied that he had been with HYMS from August 2016 with funding secured for three years if necessary.

The Sub Committee was content with the response given.

The Sub Committee asked what the planned start date of the study would be pending funding approval and REC approval.

Dr Totty replied that he planned to start recruiting in Hull as soon as possible; realistically this would be January/February 2017, pending REC approval. Recruitment will be immediately following the necessary approvals. He explained that he planned to run this as a pilot phase whilst further funding was secured, and obtain REC approval for further sites as and when they come on board. Dr Totty said that some sites had already expressed an interest but this is preliminary for the time being and he would ideally like to start recruiting as soon as possible.

The Sub Committee was content with the response given.

The Sub Committee queried that in several places in the application it is stated that the study needed MHRA approval.

Dr Totty apologised for this error and confirmed that the study did not need MHRA approval, as it was a medical device that they would be investigating.

The Sub Committee was content with the response given.

The Sub Committee noted that the protocol stated in Section 8.1.3 that patients would be randomised "via an online randomisation service (Sealed Envelope)". It asked how the online service provided sealed envelopes and how it would work across multiple centres.

Dr Totty replied that "Sealed Envelope" was an online service that offered randomisation services remotely (https://www.sealedenvelope.com). They do not provide physical sealed envelopes.

The Sub Committee was satisfied with the response given.

- **Informed consent process and the adequacy and completeness of participant information**

The Sub Committee noted that the following changes were required in the Participant Information Sheet:

- Under 'Invitation' provide alternative to 'Fellow' as few will understand this term.
- Under 'Surgical Infections' add some text about the DACC coated dressing which only otherwise is mentioned in the study title. It could be along the lines of "Both wound dressings are used in clinical practice but one has a coating (DACC) designed to trap bacteria. We shall study whether this provides additional benefit."
- Under 'What happens in the study?' the description of randomisation could be improved, phrases 'like tossing a coin" are sometimes added. In the same section it is not stated how the questionnaires at 3 and 6 months should be returned and to whom.

The applicant responded with the updated documents and the Sub Committee was content with the revised documents.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter]	1.0	20 October 2016
GP/consultant information sheets or letters [Appendix 9 - GP Letter]	1.0	17 November 2016
IRAS Application Form [IRAS_Form_17112016]		17 November 2016
IRAS Checklist XML [Checklist_24112016]		24 November 2016
Other [Case Report Form V1]	1.0	17 November 2016
Other [Screening Form]	1.0	17 November 2016
Participant consent form [Appendix 6 - Participant Consent Form]	1.0	24 November 2016
Participant information sheet (PIS) [Appendix 5 - Patient Information Sheet]	2.0	24 November 2016
Research protocol or project proposal [A randomised controlled trial to assess the clinical and cost effectiveness of Dialkylcarbamoylchloride (DACC) coated post-operative dressings versus standard care in the prevention of Surgical Site Infection in clean or clean-contaminated, vascular surge]	1.0	17 November 2016
Summary CV for Chief Investigator (CI) [Research CV George Smith]		20 October 2016

Summary CV for student [Research CV Joshua Totty]		20 October 2016
Summary CV for supervisor (student research) [Research CV IC Chetter]		20 October 2016
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flowchart of Events]	1.0	09 November 2016
Validated questionnaire [Appendix 7 - EQ5D]		
Validated questionnaire [Appendix 8 - SF36]	1.0	09 November 2016
Validated questionnaire [Appendix 11 - HPA Post Discharge Questionnaire]		06 October 2016

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

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

16/LO/2135	Please quote this number on all correspondence

Yours sincerely

Pp Dr Daryl Bendel
Chair

Email: nrescommittee.london-harrow@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Mr James Illingworth, Hull and East Yorkshire Hospitals NHS Trust, R&D Department,*

8.1.5 Appendix 5 – PHE Post-Discharge Questionnaire

Surgical wound healing post discharge questionnaire

Type of surgery _____

Date of operation ____/____/____
Date form to be completed ____/____/____

Dear Patient,
As part of the clinical trial you have entered to look at wound infections following your surgery we would be grateful if you would complete the following questionnaire and return it in the envelope provided.

Please fill in the date you completed this questionnaire ____/____/____

Have you had any problems with the healing of your wound?
☐ YES ☐ NO

If you have answered NO you do not need to continue with the rest of the form but it is very important that you return it to the hospital in the envelope provided. Thank you for taking the time to do this. If you have answered YES, please read the following carefully and complete the rest of the form.

Since you were discharged from hospital after your operation have you noticed any of the following symptoms?

Was there any discharge or leakage of fluid from any part of the wound?
☐ Yes ☐ No
If yes, was it either;
☐ Clear or blood stained
☐ Yellow/green (pus)
☐ Other-please specify _____

Please tick any of the following additional symptoms that applied to your wound:
☐ Pain or soreness in addition to the discomfort experienced following the operation.
☐ Redness or inflammation spreading from the edges of the wound.
☐ The area around the wound felt warmer/hotter than the surrounding skin.
☐ The area around the wound became swollen
☐ The edges of any part of the wound separated or gaped open.

Did any health care worker take a sample from your wound to send to the laboratory?
☐ Yes ☐ No
If you saw a health care worker because of these symptoms, please indicate who you saw from the list below-
☐ GP
☐ District nurse
☐ Midwife
☐ Doctor or nurse at the hospital
☐ Other – please specify
☐ Did not see one about my wound

Please tell us the date you noticed these symptoms.
If you cannot remember the exact date, please give an approximate date **_____/____/_____**

Have you been prescribed antibiotics for an infection in the wound?
☐ Yes ☐ No

If yes, who prescribed them? _____

Have you been re-admitted to hospital with an infection of the surgical wound?
To the hospital at which the operation was carried out? ☐ Yes ☐ No
To another hospital? ☐ Yes ☐ No
If yes, which one? _____
Other comments_____

For Office Use Only: (To be completed by surveillance co-ordinator only)
Patient reported SSI meets definition ☐ Yes ☐ No
If yes enter criteria for SSI-
☐ Criterion 1 Discharge pus + antibiotics prescribed
☐ Criterion 2 Clinical signs* + dehiscence
☐ Criterion 3 Clinical signs* + antibiotics prescribed
*Clinical signs- at least 2 of pain, heat, redness or swelling.

Note: Do not report stitch abscess (discharge confined to points of suture penetration, minimal inflammation)

CHAPTER 9: LIST OF ABBREVIATIONS/INDEX

A

AD – Anno Domini

ANOVA – Analysis of Variance

ARR – Absolute Risk Reduction

ASA – American Society of Anaesthesiologists

B

BC – Before Christ

BMI – Body Mass Index

BP – Bodily Pain

C

CDC – Centres for Disease Control and Prevention

CEA – Carotid Endarterectomy

CI – Confidence Interval

CSH – Cell Surface Hydrophobicity

CVA – Cerebrovascular accident

D

DACC – Dialkylcarbamoylchloride

E

ECM – Extracellular Matrix

EQ-5D-3L – EuroQol 5 Domains 3 Level

G

GH – General Health

GI – Gastrointestinal

GP – General Practitioner

H

HRQoL – Health Related Quality of Life

HT – Health Transition

HTA – Health Technology Assessment

I

ICU – Intensive Care Unit

IgG – Immunoglobulin G

IL-1 – Interleukin-1

IV – Intravenous

IWH – Impaired Wound Healing

M

MCS – Mental Component Score

MH – Mental Health

MODS – Multiple Organ Dysfunction Syndrome

MRSA – Methicillin-Resistant *Staphylococcus aureus*

MSSA – Methicillin-Sensitive *Staphylococcus aureus*

N

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NPWT – Negative Pressure Wound Therapy

O

OR – Odds Ratio

P

PCS – Physical Component Score

PDGF – Platelet Derived Growth Factor

PF – Physical Functioning

PHE – Public Health England

PHMB – Polyhexamethylene Biguanide

PIS – Patient Information Sheet

POD – Post Operative Day(s)

PVD – Peripheral Vascular Disease

R

RCT – Randomised Controlled Trial

RE – Role Emotional

ROS – Reactive Oxygen Species

RP – Role Physical

RRR – Relative Risk Reduction

S

SF – Social Functioning

SF-36 – Short Form 36

SIRS – Systemic Inflammatory Response Syndrome

SpO_2 – Haemoglobin Oxygen Saturation

SSI – Surgical Site Infection

T

TF – Tissue factor

TGF-β – Transforming growth factor-β

U

UK – United Kingdom

UV – Ultraviolet

V

VAS – Visual Analogue Score

VEGF – Vascular endothelial growth factor

W

WCC – White Blood Cell Count

WHO – World Health Organisation