

**DRUID**

**DRessing of diabetic foot Ulcers: Infection Deterrent trial**

**A pilot single-centre, randomised, controlled trial assessing clinical outcomes of diabetic foot ulcers managed with different wound dressing regimes.**

**Version 1.1, dd 5Nov2018**

Chief Investigator’s Statement of Ownership and Content.

I, Shona Johnston, confirm that this protocol is my work and is owned by me. The protocol conforms with standards outlined in the Declaration of Helsinki 1964.

Name (PRINT):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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**RESEARCH PROTOCOL SUMMARY**

|  |  |
| --- | --- |
| **TITLE:** | A pilot single-centre, randomised, controlled trial assessing clinical outcomes of diabetic foot ulcers managed with different wound dressing regimes. |
| **Short title:** | DRUID trial (DRessing of diabetic foot Ulcers; Infection Deterrent) |
| **IRAS number** | 250770 |
| **Device description** | |  |  |  | | --- | --- | --- | | **Treatment arm** | **Dressing(s)** | **Active element of dressing** | | A | Urgotul | TLC (technology lipido-colloid) | | B | Actilite, Urgotul SSD, Inadine (2-wk rotation in this order) | Manuka honey, silver, iodine, respectively | | C | Cutimed Sorbact | DACC (dialkylcarbamoyl chloride) | |
| **Study design** | Pilot single-centre, controlled, prospective randomized trial |
| **Primary objective** | Bioburden assessment through microbiological diagnostics at wk 0, 6, 12, and 18, focusing on any change at follow-up versus week 0 baseline figure. In addition identify bacterial species and test antibiotic sensitivity |
| **Secondary objectives** | Assessment wound size and characteristics (wk 0,3,6,9,12,18)   * Percentage healing as measured with grid. * Clinical characterisation of wound * PUSH and Texas DFU score * Visual Analogue Score for pain associated with DFU * Wound closure status   Incidence of requirement to deviate from the randomised intervention arm due to clinician-interpreted significant deterioration or improvement in foot ulcer status.  Microbiological assessment (wk 0, 3, 6, 12,18)   * Bacterial count and identification, antibiotic sensitivity   Safety of applied dressing regimes (ongoing):   * Wound infection incidence * Need for secondary interventions   Patient-reported outcome measures (wk 0, 9, 18)   * Patient mobility score (LifeSpace questionnaire) * (Wound related) Quality of life score (EQ-5D-5L and CWIQ)   Satisfaction questionnaire (wk 18)   * Patient satisfaction of comfort and impact of dressing   Status of wound (wk 26)   * Healed, not healed, recurrence, need for secondary interventions, infection incidence.   Feasibility of full RCT   * Number of eligible patients who consent to participating in the pilot trial * Recruitment to planned schedule and timelines. * Withdrawal rates * Attrition rates |
| **Patient population** | A minimum total of 45 participants, over the age of eighteen, with measurable diabetic foot ulcer, treated in podiatry clinic. Participants must have the capacity to provide informed written consent and complete patient reported outcome measures.  Treatment phase of 18 weeks  Arm A: 15 Patients will receive non-antimicrobial Urgotul dressing  Arm B: 15 Patients will receive antimicrobial dressing, each applied for 2 weeks on rotational basis (Actilite, Urgotul SSD, Inadine)  Arm C: 15 Patients will antimicrobial Cutimed Sorbact dressing |
| **Sponsor** | Cumbria Partnership NHS Foundation Trust |
| **Research grant provider** | BSN medical Limited  Willerby Hill Business Park, Block C, Willerby, Hull HU10 6FE  Contact person:  Ms Dawn Stevens, Medical Education Manager  Tel. + 44 (0)1482 670 100; Mobile + 44 (0) 7912 565 460  [Dawn.stevens@bsnmedical.com](mailto:Dawn.stevens@bsnmedical.com) |
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| **Organisation where research will take place** | Cumbria Partnership NHS Foundation Trust  Main locations:  Carleton Clinic, R&D department  Cumwhinton Drive, Carlisle CA1 3SX  Podiatry Clinics, run by Cumbria Partnership NHS Foundation Trust employed podiatrists, across North Cumbria. |
| **Planned timeline** | Recruitment start date (first patient, first visit): 1 Oct 2018,  Recruitment end date (last patient, last visit): 31 Dec 2019  Trial end date: Jan 2020 |
| **Protocol version, date** | Version 1.1, 5Nov2018 |

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LIST of abbreviations and acronyms

ABI ankle brachial index

ABPI ankle brachial pressure index

ANOVA analysis of variance

CFU colony-forming unit

CWIQ Cardiff Wound Impact Questionnaire

DACC dialkylcarbamoyl chloride

DFU diabetic foot ulcer

EQ-5D-5L EuroQol, five dimension, five question list, scale

HRA Health Research Authority

NHS National Health Service

NICE National Institute for Health and Care Excellence

NIHR National Institute for Health Research

NRES National Research Ethics Service

PROM patient-related outcome measure

PUSH Pressure Ulcer Scale for Healing

RCT randomised controlled trial

SD standard deviation

SIGN Scottish Intercollegiate Network

SSD stable silver sulfadiazine

wk week

1. Lay summary

Diabetic foot ulcers (DFU) can lead to infection and further deterioration to health. They are a considerable burden to both the NHS and the patient. The management of DFUs initially focuses on achieving wound healing. However, in many cases this objective is not met and chronic wound management then shifts its attention to avoiding infection and further complications. Clinicians have the option to treat the wound conservatively (non-antimicrobial dressings) or more aggressively (antimicrobial dressings to actively kill bacteria in the wound). At present there is a lack of data available to aid clinicians in deciding what approach is best. This study will explore if one approach is potentially better than the other in terms of reducing the risk of infection and promote wound healing. A non-antimicrobial dressing, a rotational regime of three different chemical-based antimicrobial dressings (honey, silver, iodine) and a physical antimicrobial dressing will be compared in patients over a trial period of 18 weeks per participant. In addition to recording the need to change wound management due to significant deterioration or improvement, patient and clinician satisfaction will be compared, as will infection rates and wound healing outcomes.

1. Introduction

In the UK alone, 169,000 diabetic foot ulcers (DFU) occur every year (Guest et al, 2015). The International Diabetes Federation (2005) reported that up to 70% of all leg amputations happen to people with diabetes and 85% are preceded by a foot ulcer. Furthermore, three quarters of diabetics who experience an amputation will die within five years (Schofield *et al,* 2006).Diabetes NHS (2012) estimates total National Health Service (NHS) spending on ulceration and amputation in people with diabetes in England in 2010/11 was circa 0.7% of the budget and warned as diabetic numbers grow so will this expenditure. Lipsky *et al* (2004, 2012) associated infection in DFU with high mortality, high attendance at clinics and possible risk of amputation, advising antibiotics are required for infected wounds, but there is no evidence to support issuing antibiotics for uninfected ulcers. This is a critically important topic, since the longer that healing is delayed, the higher the risk of infection developing (Hampton and Collins, 2005). To further illustrate the point concerning the impact of foot ulcers: the healing rate of DFUs is poor; on average, 24% of wounds have healed by week 12 of treatment, and only 31% at 20 weeks of treatment (Margolis, 1999). A cohort study involving 31 diabetic patients determined that the average healing time for neuropathic DFUs is 78 days whereas this increases to 133 days for patients with additional peripheral vascular disease (Zimny et al, 2002). Further analysis has shown that the size of the ulcer negatively correlates to the healing rate, whereas a patient’s age, sex, or type of diabetes is not associated with a change in healing rate outcome (Oyibo, 2001). DFU healing progress at 4 weeks of treatment is a predictor of the likelihood that the wound will be healed by 12 weeks of treatment. If the wound has not healed by at least 50% after 4 weeks, the likelihood that the DFU will be completely healed by 12 weeks is reduced to circa 10% (Sheehan, 2003). Taken together, there is a major group of patients with DFU -those with larger ulcers, and co-morbidities, responding poorly to standard treatment in the first 4 weeks – that is at risk of ending up with long-term wounds taking over 3 months to heal, if at all.

There is uncertainty concerning the optimal way to dress and manage DFUs. Lipsky *et a*l (2004) concludes there is insufficient evidence for the study to advise on a dressing product, this view being reinforced by the National Institute for Health and Care Excellence (NICE, 2015), citing the clinician needing to consider cost and appropriateness following a holistic assessment. However, it is acknowledged that in the treatment of DFUs, topical antiseptics/antimicrobials have important roles in controlling bioburden in wounds, while limiting exposure to antibiotics, and therefore reducing the risk of antibiotic resistance developing (International Working Group on the Diabetic Foot, 2015). Acute wound infection is easily diagnosed using the classic signs, including erythema, swelling, local warmth/heat and pain. More challenging is the identification of infection in chronic wounds, being subtle in nature and detected by consistent and repeated assessment (European Wound Management Association, 2005). Indiscriminate swabbing is discouraged due to financial constraints (Bowler *et al,* 2001, World Union of Wound Healing Societies, 2008) but selective swabbing can provide useful information on the presence of potential pathogens and the nature of the local microbiology.

Wound dressings traditionally contain antiseptic/antimicrobial (with the phrase ‘antimicrobial’ used hereafter) agents such as silver, honey, and iodine as well as those impregnated with polyhexamethylene biguanide, and have a broad range of antimicrobial activity which can be used to treat localised wound infection and/or to provide an impediment to microorganisms in wounds at high risk of infection or re-infection (Vowden *et al,* 2011). Antimicrobial dressings have been used extensively but two Cochrane reviews -- Vermeulen *et al* (2007) and Storm-Versloot (2010) -- concluded there was insufficient evidence to show that silver dressings improve healing rates and as a result there was a discussion on the availability and efficacy of them. Consequently, Lipsky *et al* (2012) advised topical therapy should only be recommended for superficial, mild infections and in conjunction with systemic antibiotics if severe colonisation but reiterated the dressings must only be applied when infection is evident or identified. Subsequently there appears to be a constriction on all antimicrobial usage (World Union of Wound Healing Societies, 2008, Wounds UK, 2011). There is certainly paucity in high-level evidence from randomised controlled trials concerning the efficacy of antimicrobial dressings compared to non-antimicrobial dressings in terms of infection prophylaxis and wound healing.

Each year, the NHS spends approximately £2.3bn – £3.1bn (at 2005-2006 cost) on dressings and associated products, equating to 3% of the total estimated health expenditure (Posnett and Franks, 2008). Furthermore, patients with wounds cost the NHS up to £5 billion more per annum than matched control patients (Guest et al, 2015). Regarding dressing prescriptions, silver dressings represent one seventh of wound dressing prescriptions (Iheanado, 2010), resulting in a high cost implication for the NHS. Conversely Berendt and Lipsky, (2003) argued that a dressing which protects these patients against infection will lead to better patient outcomes and reduced NHS spending, due to significant reduction in the duration of treatment and personnel costs. It should be noted that health professionals have a pivotal role in the allocation of wound care resources, therefore it is vital that their procedures/protocols are based on evidence-based practice (Gray *et al*, 2002). This raises the valid question whether more expenditure in the short term may potentially lead to long-term cost savings due to e.g. reduced incidence of infection. Again, this is something that needs to be explored through controlled trials to be able to draw concrete conclusions.

Searle *et al* (2005) ascertained that the patient’s circumstances and ability to concord with treatment plans is important in predicting foot ulceration. In both primary and secondary care DFU clinics there is a cohort of patients in whom diabetes is not well controlled. They may have issues with hygiene; fail to comply with treatment regimes or professional advice ; are poor attenders to appointments; have inadequate footwear/ offloading compliance; have cognitive, behavioural, and/or social issues (Suico et al, 1998, Searle *et al,* 2005) and in reality, a lot of the guidance fails both the clinician and the patient on how to proceed with their DFU care. Where possible, Litzelmen et *al* (1998) cites modification of these factors would lead to a reduction in foot ulceration, but in reality this is a hard task to achieve. Searle *et al* (2005) highlights the pressure the podiatrist experiences with the patient’s expectation they are responsible for healing the DFU without their own input being required. The current consensus is that clinicians should apply an inert knitted viscose primary dressing when infection is not identified (SIGN, 2013, NICE, 2015) in DFUs, however it is important that the current guidance is analysed to assess the strength of evidence which underpins these recommendations. NICE (2015) offers the guidance that when developing the care plans for patients with DFUs; clinicians need to choose the product based on the clinical assessment of the wound and take into account the person’s preference, being mindful of cost, looking to use items of the lowest acquisition charges, suitable to the clinical circumstances. But it is acknowledged that the evidence surrounding the numerous and diverse range of dressings designed for DFUs is often limited or inconclusive. On analysis of their evidence base, which due to sheer volume of data was very difficult to locate, for the use of topical antimicrobials its provenance consisted of; one very low quality RCT with 188 participants which concluded there was no significant difference between changes in ulcer size for DFUs treated with a collagen/oxygen regenerated cellulose/silver dressing or a saline gauze dressing, with another low quality meta-analysis of 2 RCTs with 224 participants trialling the same dressings confirmed this conclusion. However on looking at the evidence in depth they only listed two of the studies for analysis: Gottrup *et al* (2013) and Jeffcoate *et al* (2009). Gottrup *et al* (2013) had only 29 participants and conversely concluded that the collagen/ORC/silver normalises the wound microenvironment and protects against infection, resulting in improved wound healing. However, Jeffcoate *et al*’s (2009) larger study (n = 229) concurred with the consensus opinion (i.e. choice of dressing did not significantly affect ulcer healing rate). It is proposed that more RCTs are undertaken to explore the appropriate care DFUs require, but NICE (2015) states that alternative methodologies may also be considered in the case of treating a complex wound. It is recommended that any future proposed study should monitor and evaluate the comparative cure rates of DFUs, rates and extent of secondary (surgical) interventions, health-related quality of life, and adverse events, thus building a robust foundation to support evidence based practice. The advice has been updated with the publishing of “Chronic wounds: advanced wound dressings and antimicrobial dressings” (NICE, 2016) which recommends debridement for both infected and non-infected ulcers and that wounds need to be clean and free of excessive exudate with the choice of dressing based on individual patient assessment. Though it is acknowledged that antimicrobial agents can help to prevent infection and enhance ulcer healing, no further guidance has been issued, with the authors acknowledging there is no high quality evidence to suggest any significant differences in wound healing outcomes when comparing the various types of dressings. The evidence supporting the guidance is based on the Cochrane review by Wu *et al* (2015) who completed a systematic review of randomised controlled trial evidence on the effectiveness of dressings for healing foot ulcers in people with diabetes mellitus, including 13 systematic reviews, containing 17 relevant RCTs with one review reporting the results of a network meta-analysis, hence presenting information on indirect, as well as direct, treatment effects. There were 11 different comparisons supported by direct data and 26 comparisons supported by indirect data with four comparisons concluding, via direct data, that there was evidence of a difference in wound healing between dressing types. However the evidence was assessed as being of low or very low quality. Wu et al (2015) concluded there was no robust evidence to support a particular dressing type when treating DFUs, with practitioners needing to judge what is appropriate, taking into account cost and the patient’s views.

The aim of this randomised, controlled, prospective pilot trial is to determine and compare the wound healing efficacy of three different dressing regime approaches to DFU management. These are a) non-antimicrobial dressing, b) a rotational approach with dressings that exert an antimicrobial effect through chemical interaction with bacteria, and c) a dressing that interacts with bacteria through physical interaction. This pilot will also seek to assess the effect of these three approaches on wound characteristics, infection incidence, and patient-reported outcome measures. Furthermore, the feasibility of progression of this pilot into a full RCT will be evaluated. This will be the first time that a comparison trial of different DFU management strategies is conducted. Particular focus will be on prophylaxis of deterioration and infection of the DFU, and therefore patients who are at higher risk – including non-compliance with supporting interventions such as off-loading, the presence of co-morbidities, long-term presence of the DFU, and poorly controlled diabetes – will be enrolled in the study. The rational for a rotational approach with the chemical antimicrobial dressings, is because both silver and iodine dressings are not recommended for continuous long-term use (Silver et al, 2006; Sibbald et al, 2011). There are concerns about bacterial resistance to silver in particular, and concerning the physiological effects of long-term systemic exposure to iodine. The use of Manuka honey dressing as part of the rotation of chemical antimicrobial dressings allows periods of non-exposure to silver and iodine.

1. Investigational deviceS

Three different dressing regimes will be applied, and one of these regimes will utilise three different dressings. Therefore, a total of five different dressings will be utilised. Table 1 summarises the dressing regimes setup. Apart from Cutimed Sorbact, provided free of charge by BSN Medical as part of the non-restricted research grant for this study, all dressings will be purchased by the podiatry team via the conventional Trust NHS supply chain. The dressings used in this study are first-line product listed in Cumbria Partnership NHS Trust’s current wound formulary (Appendix 4).

*Table 1, Different treatment arms and dressings used for each regime*

|  |  |  |
| --- | --- | --- |
| **Treatment arm** | **Dressing(s)** | **Active element of dressing** |
| A | Urgotul | TLC (technology lipido-colloid) |
| B | Actilite, Urgotul SSD, Inadine (2-wk rotation in this order) | Manuka honey, silver, iodine, respectively |
| C | Cutimed Sorbact | DACC (dialkylcarbamoyl chloride) |
| A,B,C | Tegaderm Foam Adhesive | Secondary dressing for all arms. |

* **Urgotul**

Urgotul is marketed by Urgo Medical (<http://www.urgo.co.uk/67-urgotul>). Its active element is TLC (technology lipido-colloid) which is designed to promote wound healing. When it comes in contact with exudate, Urgotul dressing gels and creates a moist environment, aimed at promoting wound healing. It does not, however, have antimicrobial properties.

* **Actilite**

Actilite is marketed by Advancis medical in the UK (<http://www.advancis.co.uk/products/activon-manuka-honey/actilite>). The antimicrobial ingredient of Actilite is Manuka honey. In the honey itself, it is believed that the main active ingredient is hydrogen peroxide which kills bacteria by creating reactive oxygen (Bang et al, 2003). Manuka honey has previously been shown to accelerate DFU healing and reduction of bacterial burden in the wound (Kamaratos et al, 2012). The (comparative) effectiveness of Actilite has not been determined, though some case series have been published on the Advancis product website; favourable outcomes were achieved for patients managed with said dressings. A recent paper demonstrated that Manuka honey – the active ingredient in Actilite - is the most antibacterial type of honey against S.aureus (Almasaudi, 2017).

* **Urgotul SSD**

In the UK, Urgotul SSD is is marketed by Urgo Medical (<http://www.urgo.co.uk/70-urgotul-ssd>). The dressing uses silver contained in a salt, and the mechanism of action is through sustained release of Ag ions as the salt is exposed to wound exudate (Teot, 2005). A recent consensus on the appropriate use of silver dressings described the main roles of silver dressings, such as Urgotul SSD, in the management of wounds to be the reduction of bioburden and to act as an antimicrobial barrier (Wounds International, 2012a and 2012b). The consensus document recommends that silver dressings be used initially for a two week 'challenge' period. At the end of the two weeks, the wound, the patient and the management approach should be re-evaluated (Wounds International 2012a). There is evidence that silver dressings can reduce bioburden and may aid wound healing, however evidence from comparative trials involving other types of dressings and longer follow-up periods are lacking (Carter et al, 2010).

* **Inadine**

In the UK, Inadine is marketed by Systagenic (<http://www.systagenix.co.uk/our-products/antimicrobial/inadineandtrade-dressing-204> ). It is a knitted viscose dressing that is impregnated with 10% povidone iodine (also known as Betaisodona), which equates to 1.0% available iodine. Apart from killing bacteria through attacking proteins and lipids within the bacteria, iodine also inhibits the release of bacterial exotoxins and tissue-destructive enzymes and cytokines (König et al, 1997). One disadvantage of iodine-based dressings is that their use is contraindicated with: known hypersensitivity, thyroid disease, pregnancy & breastfeeding, and renal impairment. Jeffcoate et al (2009) previously showed that Inadine is non-inferior to Aquacel, another proprietary wound dressing, but also non-superior to standard kniotted viscose dressing for healing of chronic wounds. Overall, Inadine has been shown to be well tolerated by patients (Campbell, 2013).

* **Cutimed Sorbact**

An alternative to the traditional antimicrobials is dialkylcarbamoylchloride (DACC) -coated gauze sold under the commercial name of Cutimed® Sorbact® (BSN Medical), previously named Cutisorb® Sorbact® and still marketed under that label in some countries. Most bacteria and fungi found within a wound are hydrophobic and in the moist environment of a wound, bacteria and fungi irreversibly bind to the hydrophobic fatty acid coating on the dressings, with no chemical active ingredient interfering with normal cell biochemistry (Ljungh *et al*, 2006). This principle has been utilised in the wound care environment to provide an alternative approach to reducing bioburden (Probst *et al,* 2012). Furthermore, the more pathogenic the bacteria the more hydrophobic they tend to be (Ljungh *et al*, 2006) and once they are bound to the DACC coating they are unable to migrate or multiply. It is hypothesized that pathogens are effectively trapped but not killed; endotoxins are not released into the wound bed resulting in improvement in the management of bioburden (Cooper, 2009). Hence it has been postulated that wounds may heal efficiently without the interruption of pathogens, reducing risk of critical colonisation, thus reducing costs to the NHS. Problems associated with other types of antimicrobial agents, such as patient sensitisation, bacterial resistance, or skin staining (Hampton, 2007) should not occur due to the physical rather than chemical action of the dressing. Von Hallern and Lang (2005) examined if Cutimed® Sorbact® constitutes a reasonable alternative to the current procedure for wound treatment for chronic, contaminated, colonised and infected wounds. They analysed 418 wound swab microbiology reports over a 22 month period to question if a dressing, which has no antimicrobial content but rather relies on a hydrophobic physical property, can reduce the microbial count without interrupting the normal wound healing process and enable the dressing to be removed without causing trauma or pain. They concluded that Cutisorb® Sorbact®is an effective dressing in wound care, with no allergic reactions or hypersensitivity noted and infection regressed within the same timescale as when conventional antimicrobials were used. The team measured a quantitative decrease in bacterial strains within the wounds. Patients also reported a lack of pain associated with the change of dressing.

**Medical Device management**

Dressings will be stored in the podiatry clinic rooms at the temperature recommended by the respective manufacturers. No requirement for involvement pharmacy or clinical trials pharmacist. Standard available stocks of dressings to be used, including Cutimed Sorbact provided free of charge by BSN Medical as part of the research grant.

1. Study hypothesis
   1. Primary objective

Bioburden assessment through microbiological diagnostics at wk 0,3,6,12,18, focusing on any change at follow-up versus week 0 baseline figure. In addition identify bacterial species and test antibiotic sensitivity.

* 1. Secondary objective

Assessment wound size and characteristics (wk 0,3,6,9,12,18)

* Clinical characterisation of wound
* PUSH and Texas DFU score
* Wound grid measurement, comparison between three treatment arms in degree of wound healing - measured in % change in cm2 - between week 0 and weeks, 3, 6, 9, 12, 18 respectively
* Wound closure status
* Wound depth

To determine the incidence of requirement to deviate from the randomised intervention arm due to significant deterioration or improvement in foot ulcer status, as determined by the treating clinician.

Safety of applied dressing regimes (ongoing):

* Wound infection incidence
* Need for secondary interventions
* Reactions to application of dressing

Patient-reported outcome measures (wk 0, 9, 18)

* Patient mobility score (LifeSpace questionnaire)
* (Wound related) Quality of life score (EQ-5D-5L and CWIQ)
* Visual Analogue Score for pain associated with DFU

Satisfaction questionnaire (wk 18)

* Patient satisfaction of comfort and impact of dressing

Status of wound (wk 26)

* Healed, not healed, recurrence, need for secondary interventions, infection incidence.

1. Study protocol
   1. Study design and timeline

This concerns a single centre, controlled prospective randomized study. The study will be carried out in Cumbria by NHS Cumbria Partnership NHS Foundation Trust. The study will take place in a local community setting with support and oversight from a senior podiatrist, the wider podiatry team and research staff. Research delivery staff will be delegated to provide support with data collection and processing. Table 2 outlines the planned timeline.

*Table 2. Anticipated timeline*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Month | Setup | Recruitment | Analysis | Finalise |
| July-18 | Submission for HRA approval |  |  |  |
| Aug-18 | NIHR portfolio adoption |  |  |  |
| Sep-18 | HRA and Trust approval |  |  |  |
| Oct-18 |  | Start recruitment |  |  |
| Jul-19 |  | Finish recruitment |  |  |
| Dec-19 |  |  | Follow-up complete; Analyse data |  |
| Jan-20 |  |  |  | Manuscript & report writing |
|  |  |  |  |  |

* 1. Participant identification and research setting

Participants will be recruited from podiatry clinics and all eligible patients will be invited to take part until the required numbers have been achieved. Identification will be by the podiatrists who are supporting the study. A screening form will be completed for potentially eligible patients to confirm that they indeed meet the trial criteria.

The podiatry teams in Cumbria will be supporting this study, and the study will initially take place in Carlisle, to be followed by clinics in Whitehaven, Workington, Cockermouth, Penrith and Wigton. All research activity and also treatment as usual (ie application of dressings) will take place in these clinic settings.

To summarise, the podiatrists will:

* Identify potentially eligible patients and ask verbal consent for them being approached about the study by a member of the R&D team
* Complete the incl/excl criteria part of the screening form
* Apart from treatment as usual activities (dressings, cleaning of wound, footwear advice), measure the wound size and complete the PUSH and SINBAD score once a patient has consented to taking part (informed consent will be taken by members of delegated R&D team, or one of the podiatrists as long as they are listed on the delegation log).
  1. Consent

Those eligible will be approached and provided with an information pack and consent form, which will be signed to indicate that informed consent has been given. Patients will be given ample time to consider taking part, more than 24 hours if they wish. The direct healthcare professional will first approach a patient about the study, and after verbal consent by the patient the healthcare professional themselves or a member of the research team can go through the informed consent process.

Upon randomisation, the treatment with the allocated dressing regime can commence. This can be at the same visit as when the consent process takes place or at the next clinic visit if there is not sufficient time or the randomisation allocation has not yet been obtained. **The start of the application of the allocated dressing is the trial start date**.

Participants will receive no incentives and consent will be regarded as a process and not a one-off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard of care will not be affected by either declining to participate in the study or withdrawing during participation. Data collected up to the date of withdrawal will be retained for analysis.

* 1. Recruitment

Participants will be randomised to one of three arms, see Table 1, for 18 weeks or until ulcer healing has been achieved (if the latter occurs then they will still be followed up according to the study schedule). All participants will have demographic data obtained and a number of baseline and follow-up measures, see Table 3.

*Table 3. Overview of study measurements*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Weeks | 0 | 3\* | 6\* | 9# | 12# | 18~ | 26~ |
| Clinical characterization of wound | X | X | X | X | X | X |  |
| Ulcer size (Coloplast grid) | X | X | X | X | X | X |  |
| PUSH score | X | X | X | X | X | X |  |
| Texas DFU grading score | X | X | X | X | X | X |  |
| Wound closure status | X | X | X | X | X | X |  |
| Microbiology swab testing | X | X | X |  | X | X |  |
| VAS pain scale | X |  |  | X |  | X |  |
| QoL CWIQ | X |  |  | X |  | X |  |
| QoL EQ-5D-5L / LifeSpace | X |  |  | X |  | X |  |
| Patient experience questionnaire |  |  |  |  |  | X |  |
| Wound status (long-term) |  |  |  |  |  |  | X |

*\* Allowed to be up to 1 week early or late*

*# Allowed to be up to 2 weeks early or late*

*~Allowed to be up to 3 weeks early or late*

The Pressure Ulcer Scale for Healing (PUSH) tool is a standardised method of assessing and monitoring the severity and healing of both pressure ulcers and venous leg ulcers, and is also applied for foot ulcers (Stotts et al, 2001; Ratliff & Rodeheaver 2005). The Pressure Ulcer Scale for Healing (PUSH) is a valid, responsive, evaluative tool to monitor and document wound progress of foot ulcers (Hon, 2010). Findings also suggest that total PUSH scores predict time-to-heal for foot ulcers (Gardner 2011). The Texas wound grading score is well established in DFU management (Armstrong et al 1998). The grading is as follows:

* Grade 0 – pre-or postulcerative site that has healed
* Grade 1 – superficial wound not involving tendon, capsule, or bone
* Grade 2 – wound penetrating to tendon or capsule
* Grade 3 – wound penetrating bone or joint

Within each wound grade there are four stages:

* Stage A – clean wounds
* Stage B – non-ischemic infected wounds
* Stage C – ischemic noninfected wounds
* Stage D – ischemic infected wounds

A mobility measure will be taken using the life space questionnaire (Stalvey *et al* 1999). This is a tool that has demonstrated reliability and construct and criterion validity in establishing the spatial extent of an older person’s mobility within their home setting. There are other versions (Peel *et al* 2005) that additionally measure the use of aids and equipment however this is not of particular interest within the study, hence the simpler version will be used.

* 1. Follow-up

Patients are in the study for a period of 18 weeks. Thereafter, the patient will be followed up as they would be in normal clinical practice. During and after the trial, clinical staff will redress the wound as per routine care, and during the trial they will conduct the measurement of the foot ulcer (grid measurement tool, SINBAD grading and PUSH score). The researcher will be in attendance at week 0, 3,6,9,12 and 18 of study participation to randomise the patient and conduct/collect the study participant questionnaires. The researcher will phone the participant at week 26 to check on wound status and any adverse event reporting.

* 1. Outcome measures
     1. Primary outcome measures

The primary outcome for this trial will be the bioburden in the index DFU, as measured by microbiological diagnostics at wk 0,3,6,12,18. The bacterial load will be quantified using the following formula: bacterial load (CFU/g) = (number of CFUs on plate ×103) / dilution. This will be performed for aerobic and anaerobic cultures.

Any change at follow-up versus week 0 baseline figure will be calculated. In addition identify bacterial species and test antibiotic sensitivity. The bacterial species will be identified by standard microbiological techniques, including gram stain and microscopic examination, and trial specimen samples will be processed and analysed in the same microbiology laboratory where regular samples are sent, per Trust standard operating procedures.

Levine’s technique will be applied for swabbing of the wound (Levine et al, 1976). Samples, taken with a sterile cotton swab and placed in containing charcoal transport medium, will be sent to the laboratory asap. Wound swabs should reach the laboratory on the day that they are taken, but in exceptional circumstances can be stored in a specimen fridge overnight. Specimens must not be left over the weekend or bank holidays.

* + 1. Secondary outcome measures

This study also aims to record wound characteristics and patient-related outcomes measures, as well as safety endpoints.

Assessment wound size and characteristics (wk 0,3,6,9,12,18)

* Foot ulcer size, measured with Coloplast grid tool (week 0, 3, 6, 9, 12, 18), with week 18 being primary outcome measure.
* Clinical characterisation of wound (incl. erythema, purulence, odour, plus depth)
* PUSH and Texas DFU score
* Wound closure status and incidences of adverse events
* Wound depth

Incidence of requirement to deviate from the randomised intervention arm due to significant deterioration or improvement in foot ulcer status, as determined by the treating clinician (see also Appendix 1).

Microbiological assessment (wk 0, 6, 12, 18)

* Bacterial count and identification, antibiotic sensitivity

Safety of applied dressing regimes (ongoing):

* Wound infection incidence
* Reaction to dressing
* Need for secondary interventions (incl. need for surgery, admission to hospital, iv antibiotics)

Patient-reported outcome measures (wk 0, 9, 18)

* Patient mobility score (LifeSpace questionnaire)
* (Wound related) Quality of life score (EQ-5D-5L and Cardiff Wound Impact Questionnaire)
* Visual Analogue Score for pain associated with DFU

Satisfaction questionnaire (wk 18)

* Patient satisfaction of comfort and impact of dressing

Feasibility of full RCT

* Number of eligible patients who consent to participating in the pilot trial
* Recruitment to planned schedule and timelines.
* Withdrawal rates
* Attrition rates

1. Subjects
   1. Anticipated number of research subjects

There is no pilot data to base a *priori* sample size calculation on and therefore this study is a feasibility trial to determine the indicative effect size achieved when comparing the three arms.

One of the secondary outcomes, average percentage decrease in ulcer size between baseline and 18 week follow-up is used for sample size calculation – this calculation is primarily for illustrative purposes only, since this current pilot study is not intended to achieve sufficient statistical power to detect significant differences between the different treatment arms . Table 5 below merely presents numbers required on the basis of hypothetical outcomes. Treatment arms X, Y, and Z are used rather than this trial’s arms A, B, and C, to avoid any assumptions regarding dressing regime performances. Furthermore, it is also recognised that the current total sample of 45 participants is insufficient to make this current pilot trial powerful enough. The sample size calculations are therefore illustrative, and analysis of data from this current pilot study will inform power calculations for a potential full RCT.

Power calculations for sample size, 80% power, 5% significance, and SD of 30%, based on one-way Analysis of Variance (ANOVA). A priori power calculations using GPower 3.1 software, result in the following sample size summarized in Table 4. The samples sizes do not take into account attrition rates due to loss to follow-up or patient withdrawal before week 18 (incidence of this is a secondary outcome measure). An intention-to-treat approach will be applied.

*Table 4, sample size numbers required, based on hypothetical differences between treatment arms*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Treatment Arm X** | **Treatment Arm Y** | **Treatment Arm Z** | **Sample size required** |
| Degree of healing at week 18 (vs week 0) | 50% | 50% | 80% | 48 |
| 50% | 50% | 70% | 102 |
| 40% | 50% | 70% | 60 |

The CONSORT guidelines require a statement on the number of patients assessed for eligibility (Schulz, Altman & Moher 2010). The number of patients screened but who did not meet the inclusion criteria or who declined to participate will be recorded, as will any patients who are lost to follow-up (Appendix 3).

The patient attrition rate (withdrawal and loss to follow-up) will also be recorded, since this involves a study with at multiple visits, albeit incorporated into standard clinical appointments. Patients will be recruited from the adult (age 18+) population routinely seen by the evaluating clinical staff members.

* + 1. Randomisation

Following written consent, at week 0, participants are allocated at random to one of the three arms in a 1:1:1 fashion. A randomised sequence from the freeware randomisation programme, see <https://www.randomizer.org/> will be used to obtain the randomised list..

Since the eligible patients with DFUs have chronic wounds, there is ample time for the patient to decide whether to take part or not, and to allocate a randomisation arm once the patient has provided written informed consent.

When the patient has provided written informed consent the treating podiatrist will either phone (tel 01228 602173) or e-mail ([research@cumbria.nhs.uk](mailto:research@cumbria.nhs.uk) ) the research department for the next allocation. This allocation will be provided by the co-investigator for the trial, Dr Leon Jonker, who does himself not see DFU and DRUID patients. The randomisation list will only be seen by Dr Leon Jonker and a nominated member of staff, again not involved in the DRUID trial, who will deputise in his absence for annual leave.

At this stage the relevant dressing treatment regime will commence. For Arm B (rotation), the order will be Actilite, Urgotul SSD, each for 2 weeks and then same order again beyond week 6.

As the study involves administration of easily recognisable dressings it is not possible to achieve blinding for neither the participants or the researchers – it is recognised that this increases the risk of bias.

* 1. Eligibility criteria
     1. Inclusion criteria
* Clinical diagnosis of a Diabetic Foot Ulcer, present on area that is measurable with a grid sheet (this can include plantar, calcaneus, dorsal, hallux, apex, toe, or ankle-based ulcers). This includes DFU, peripheral arterial disease related wound, or other aetiology. Ulcer should not penetrate the tendon, periosteum or bone.
* DFU present for at least 6 weeks.
* Adult patients aged > 18 years
* Mental capacity to give consent
* A diagnosis of either Type I or Type II diabetes, plus at least one of the following factors:
  + Poorly controlled diabetes (Hba1c > 8% / 64 mmol/mol measured within last 6 months)
  + Neuropathy
  + Multiple concurrent foot ulcers
  + Recurrence of wound(s) within 3 months of last point that wound healed.
  + Peripheral arterial disease
  + Poor compliance with best practice in foot ulcer management, including non-optimal use of off-loading device.
    1. Exclusion criteria
* Under the age of 18 years
* Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity
* Limited life expectancy, i.e. undergoing palliative care
* Active infection in foot ulcer that cannot be managed in podiatry service (ie requires specialist secondary care intervention)
* Currently receiving antibiotics (topical or systemic), or within one week of receiving antibiotics.
* Patients who are participating in another research study involving an investigational product that is related to the DFU or a co-morbidity that may influence wound healing (incl diabetes, peripheral arterial disease, or immune disorders).
* The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives.
* Foot ulcer in area of the foot which would make ulcer size measurement impossible.
* Patient pregnant, actively planning to become pregnant, or lactating
* Ankle brachial index < 0.6, measured within 3 months of baseline visit (if ABPI cannot be established due to diabetes complications, and podiatrist is confident – on basis of clinical information - that ABPI is >0.6 then patient can be enrolled).
* Any condition that is contraindicated for the use of any of the dressings used in this trial. This includes the earlier mentioned pregnancy, but also severe renal impairment (< 30 ml/min/1.73m2, see <https://bnf.nice.org.uk/guidance/prescribing-in-renal-impairment.html> ), and concomitant use of lithium. Thyroid disease is not a contraindication if used for short periods, ie 2 weeks at the time with 4 weeks of non-iodine exposure, unless explicitly stipulated by a clinician.
  1. Early withdrawal of subjects

Patients have the right to withdraw from the trial at any time and without giving any reason. If a patient withdraws from the trial, any and all information gathered prior to the withdrawal will be excluded in the analysis, no further data collection will occur. If a patient does not attend a planned follow-up appointment then two more attempts will be made to contact the patient regarding the study. If still no contact can be made then the patient is deemed lost to follow-up and any collected study data will be retained.

If a female patient finds out that she is pregnant during the course of participating in the study, they will be requested to inform the research team immediately. The participant will be withdrawn from the study if allocated to the rotation dressing arm (arm B). Since the study is not blinded, there is no requirement for an unblinding procedure.

Due to the study design, patients may also be withdrawn from the study intervention on clinical grounds. This is not a withdrawal from the study, but a (temporary) withdrawal from the trial intervention. Appendix 1, Intervention Deviation, summarises that particular process.

1. Safety
   1. Potential risks & benefits to study participants

There is no anticipated personal safety risk associated with taking part in this study. If the research team learns of important new information that might affect the patient’s desire to remain in the study, he or she will be told. Appropriate precautions are in place to ensure medical and personal information is kept safe through adhering to appropriate governance regulations. Any adverse events will be recorded, as outlined in sections below.

For the participants in the control group there is no direct benefit in taking part in this study. They will be cared for in exactly the same manner as they normally would. For participants there may be benefits in terms of improved foot ulcer healing – however, at present it is not known which of the three dressing regimes may achieve more favourable results. This study is aimed to assess this. Participants cannot claim payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

* 1. Safety definitions

|  |  |
| --- | --- |
| Adverse Event (AE) | Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.  An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device. |
| Serious Adverse Event | A serious adverse event is any untoward medical occurrence that:   * results in death * is life-threatening * requires inpatient hospitalisation or prolongation of existing hospitalisation * results in persistent or significant disability/incapacity * consists of a congenital anomaly or birth defect.   Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |

* 1. Procedures for recording adverse events

All AEs need to be reported to the sponsor/host Trust R&D within one week of the investigator team becoming aware of them. For this purpose an AE report form is completed by the researcher and/or Chief Investigator. SAEs should be reported within one working day of becoming aware of the event, where possible.

The relationship of each adverse event to the trial must be determined by the Chief Investigator, a medically qualified individual, according to the following definitions:

* **Related**: The adverse event follows a reasonable temporal sequence from swabbing. It cannot reasonably be attributed to any other cause.
* **Not Related**: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.
* **Severity grading**: the Chief Investigator will also record if it concerns an AE or SAE.

This is recorded on the aforementioned AE reporting form. The forms are stored in the study site file.

Pseudo-anonymised copies of all adverse events forms will be shared with BSN Medical as soon as causality reporting has been performed and concluded.

1. Statistical consideration and data analysis plan
   1. Analysis of baseline characteristics

To determine the demographics and characteristics of the patients in the two arms the following data will be collated:

* Age
* Gender
* BMI
* Smoking status
* Diabetes status
* Use of medication that may impact on wound healing, incl immunosuppressants
* Significant comorbidities, including peripheral arterial disease, heart failure, pretibial oedema.
* Aetiology, chronicity, and location of wound
* Presence of diabetes, and if so length of having condition
* Neuropathy
* Offloading of the foot ulcer (yes/no, and if yes, patient-reported compliance)
* HBa1c (measured within last 6 months; only if diabetic)
* Ankle-Brachial Index value (measured within last 3 months)
* Wound infection or not (or infected at any stage of participation)

Any differences in distribution will be established with Chi-squared test or ANOVA as indicated.

* 1. Primary outcome statistics

The primary outcome for this trial will be the bioburden in the index DFU, as measured by microbiological diagnostics at wk 0,3,6,12,18. Mainly descriptive statistics will be deployed to describe the type of bioburden for each patient, and how this may change over time. The average bioburden (ie CFU/g) for each treatment arm will be compared to the other treatment arms. Any % change in bioburden will also be computed and compared. The Kruskal-Wallis test will be applied to test for any significant differences in the median for each arm, assuming data will not be normally distributed.

Bacterial species and sensitivity to antibiotics will be summarised descriptively with summary tables.

* 1. Secondary outcome statistics

The average baseline demographics for participants in each group will be compared to ascertain that randomisation has indeed led to comparable distribution of participants’:

Sex, age, HbA1c level, baseline wound size (cm2), PUSH score, Texas DFU grading score, mobility score, VAS pain score, EQ5-5D-5L score, CWIQ score, duration of wound (weeks), neuropathy status, ischaemia status.

The average difference in healing rate of foot ulcers (as measured with Coloplast 1cm square measuring grid ) between week 0 and 18 time points will be calculated per treatment arm, though weeks 3, 6, 9 and 12 will also be analysed. To compare the groups, one-way ANOVA will be applied.

Other clinical parameters will be recorded too, since they are known to be significantly associated with non-healing of foot ulcers: diabetes status, peripheral arterial disease, heart failure, pretibial oedema (Prompers et al, 2008)

One outcome aspect that will be recorded is the incidence of requirement to deviate from the randomised intervention arm, due to significant deterioration or improvement in foot ulcer status, as determined by the treating clinician. This will result in the following table, Table 5.

*Table 5, deviation outcomes*

|  |  |  |  |
| --- | --- | --- | --- |
| *Allocation*  */*  *Outcome* | **Treatment arm A**  (Urgotul) | **Treatment arm B**  (2-wk rotation, antimicrobial) | **Treatment arm C**  Cutimed sorbact) |
| No deviation from allocated regime | N | N | N |
| Deviation from allocated regime (improvement) | N | N | N |
| Deviation from allocated regime (deterioration) | N | N | N |
| *total* | 15 | 15 | 15 |

The Chi-squared test will be applied to the above cross-tabulation to determine if there is a significant difference in distribution of treatment outcomes.

To evaluate the wider effects of the different dressing regimes on foot ulcer healing, the following parameters will be compared (median difference between week 0 and different follow-up time points):

* PUSH score
* SINBAD grading score
* Mobility score (Life-Space)
* Visual analogue pain score
* EQ5-5D-5L score
* CWIQ score

To compare the groups, Mann-Whitney U-test will be applied, since data will most likely not be normally distributed.

Cox proportional hazards regression analysis will be conducted to investigate the role of the dressing regime choice and other covariates (as mentioned above, including aetiology, diabetes etc) in wound healing rates.

1. Data handling and monitoring

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who does not have a substantive contract with Cumbria Partnership NHS Trusts will need to apply for a letter of access via the NIHR research passport scheme, should they require access to identifiable study data.

Patient identifiable data will only be used within each respective Trust and by the core research team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files. The requirements of the Data Protection Act and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP.  Participants’ GP practices will be informed that they are taking part in the study.

All paper data will be held in secure locked environments in the office of the Research & Development department in the Carleton Clinic, Carlisle, Cumbria Partnership. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Upon completion of the study the site files will be archived for a period of 10 years in line with local archiving policy and procedures. Direct access to data only will be granted to authorised representatives from the sponsor / host institution, grant funder and medical device provider (BSN Medical) and the regulatory authorities to permit trial-related monitoring, audits and inspections.

This investigator-initiated trial will be monitored in terms of conduct of the study by the in-house research team, led by the Chief Investigator, who will convene on a monthly basis in person or via phone/e-mail. A trial steering committee will not be convened for this trial. The study can be audited by the in-house R&D department as part of their rolling audit programme of sponsored and hosted research studies. As part of the research grant agreement, anonymised study data will be shared with BSN Medical for review and for potential publication purposes. No identifiable data, including on potential exemplar case photos, will be contained in any of this data.

1. Goverance of study
   1. Approvals

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures

* 1. Sponsor & Indemnity

Cumbria Partnership NHS Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. BSN Medical has provided a grant for this study by means of provision of the Cutimed Sorbact dressing free of charge and a monetary grant worth £7196.

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since patients are seen at their home by community nurses or in clinic as part of their normal care pathway.

1. Publication and data-sharing policy

The study will be registered on ISRCTN or Clinical Trials Gov website, if study is adopted onto NI@HR Portfolio, in line with CONSORT guidelines on good practice in clinical research.

The results of this study will potentially be disseminated through:

* Peer-reviewed manuscript in scientific journal
* Internal report to the funder of the trial, BSN Medical Limited

As stated in the PIL and ICF, anonymised study data will be shared with BSN Medical Limited as part of the research grant agreement.

A summary of the main findings can be supplied to participants on request and this will be stated in the informed consent form.

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Appendix 1. INTERVENTION DEVIATION

As indicated, the primary objective of this study is to record incidences of significant improvement or deterioration of the index wound. This then necessitates a change in dressing intervention. The two outcome scenarios are outlined below. The decision whether or not there is a significant change of the wound’s characteristics lies with the treating podiatrist. There are no quantifiable cut-off numbers or clinical indicators associated with the decision, since each patient may start from a different baseline.

**Significant improvement of index wound.**

Examples are:

* Wound has healed. In this instance the patient will remain in the study for follow-up purposes (e.g. questionnaires at week 18, 26) but will no longer require dressings.
* If a wound is healing to such an extent that – according to the treating podiatrist - antimicrobial dressings are no longer indicated or deemed effective. For example, if wound size has reduced dramatically and is virtually healed.
* Improvement in wound associated with increase in dryness or exudate, which necessitates use of more hydrating or absorbent dressing, respectively.

If wound subsequently would benefit from return to original allocated dressing regime than that is allowed and the time elapsed will be recorded. The total trial period will not change for the patient.

Example: dressing A for 6 weeks, followed by dressing for high exudate for 4 weeks, then followed by further 8 weeks of dressing A (total trial period unchanged at 18 weeks).

**Significant deterioration of index wound.**

Examples are:

* Wound has become infected or critically colonised and treating podiatrist feels that current dressing regime is not helping to counteract the bacterial load (see also use of antibiotics during trial).
* Deterioration in wound associated with increase in slough, which necessitates the use of a more absorbent dressing.
* Deterioration in wound associated with increase in necrosis, which necessitates the use of a dressing that promotes hydration.
* Adverse reactions to dressings will also be classed as a significant deterioration of the index wound in terms of subsequent wound management.

With significant deterioration of an index wound, the patient will not return to the originally allocated dressing (ie treatment arm). The treating podiatrist can select another dressing (including dressings used before or available in the other arms) following remedial action of the deterioration.

The subsequent dressing choices and management post-Intervention Deviation event will be recorded. Patients will still be followed up at the indicated time points and asked to complete PROMs questionnaires, plus microbiology samples will be taken at the predetermined time points.

**Use of antibiotics during trial**

Since this constitutes a deterioration of the index wound, the same approach will be taken as with the other significant deterioration examples above. Regardless of whether topical or systemic (oral or iv) antibacterial treatment is required, the patient will effectively stop participating the originally allocated treatment arm.

With significant deterioration of an index wound, the patient will not return to the originally allocated dressing (ie treatment arm). The treating podiatrist can select another dressing (including dressings used before or available in the other arms) following remedial action of the deterioration.

The subsequent dressing choices and management post-Intervention Deviation event will be recorded. Patients will still be followed up at the indicated time points and asked to complete PROMs questionnaires, plus microbiology samples will be taken at the predetermined time points.

Appendix 2. study participant Flowchart

Screening

Patient identified by clinical staff member

Verbal consent requested to explain study

Patient Information Sheet is provided to patient

Screening

Patient identified by clinical staff member

Consent requested to explain study

Screening form completed

During week 0, 3, 6, 9, 12, 18 visit, following data is obtained:

* Foot ulcer size measured with grid tool
* PUSH score and Texas DFU score, and wound healed status
* Microbiology swab test (0, 3, 6, 12 and 18 weeks only)
* LifeSpace Mobility score (0, 9 and 18 weeks only)
* QoL generic, EQ-5D-5L (0, 9 and 18 weeks only)
* QoL wound, CWIQ (0, 9 and 18 weeks only)
* VAS pain for wound (0, 9 and 18 weeks only)

18 weeks (+/- 3 week window)

Patient satisfaction questionnaire regarding dressing use

26 weeks (+/- 3 week window)

Remote wound status assessment (long-term)

Patients are randomised

Consent process, baseline measures

Patients have sufficient time to consider the study and ask questions; Consent is obtained.

Ulcer size measured with grid tool; PUSH score, Texas DFU score

Patient ineligible

Patient declines to participate

0 -18 weeks: Intervention phase

|  |  |  |
| --- | --- | --- |
| **Treatment arm** | **Dressing(s)** | **Active element of dressing** |
| A | Urgotul | TLC (technology lipido-colloid) |
| B | Actilite, Urgotul SSD, Inadine (2-wk rotation) | Manuka honey, silver, iodine, respectively |
| C | Cutimed Sorbact | DACC (dialkylcarbamoyl chloride) |

Screening

Appendix 3. CONSORT Flowchart

**Screening phase**

Assessed for eligibility (n= )

Excluded (n= )

  Not meeting inclusion criteria (n= )

  Declined to participate (n= )

  Other reasons (n= )

Informed consent (n= )

Excluded (n= )

  Not meeting inclusion criteria, including insufficient healing (n= )

  Lost to follow-up (n= )

  Other reasons (n= )

Assessed for eligibility for intervention phase (n= )

**Intervention phase (Randomized)**

Allocated to physical antimicrobial intervention (n= )

 Received allocated intervention (n= )

 Did not receive allocated intervention (give reasons) (n= )

Allocated to chemical antimicrobial intervention (n= )

 Received allocated intervention (n= )

 Did not receive allocated intervention (give reasons) (n= ) – not applicable

Allocated to standard care (n= )

 Received allocated intervention (n= )

 Did not receive allocated intervention (give reasons) (n= ) – not applicable

**Follow-Up**

Lost to follow-up (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

**Analysis**

Analysed (n= )  
 Excluded from analysis (give reasons) (n= )

Analysed (n= )  
 Excluded from analysis (give reasons) (n= )

Analysed (n= )  
 Excluded from analysis (give reasons) (n= )

\**Based on CONSORT Flowchart*

Appendix 4, Cumbria Partnership NHS FT Wound Formulary for Podiatry (2016)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Necrotic** | **Sloughy** | **Granulating** | **Epithelialising** | **Infected/Critically Colonised** |

Tissue Ttype

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Debride, rehydrate and remove eschar | Remove slough  Provide clean base for granulation tissue | Promote granulation. Provide healthy  base for epithelialisation | Promote epithelialisation and  wound maturation | Manage bacterial burden |

Treatment Aim  
 **Primary Dressing Secondary Dressing Primary Dressing Secondary Dressing Primary Dressing Secondary Dressing Primary Dressing Secondary Dressing**  **Primary Dressing Secondary Dressing**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Low Exudate  ActiFormCool®  Algivon  Moderate Exudate | Mepilex® XT Border  Mepilex® Border Lite Tegaderm™ Foam Adhesive  Allevyn Adhesive | Algivon  ActiFormCool®  AQUACEL® Extra™  Sorbsan®  PolyMem  Suprasorb | Mepilex® XT Border  Mepilex® Lite  Tegaderm™ Foam Adhesive  Allevyn Adhesive | Adaptic Touch®  Urgotul  AQUACEL® Extra™  PolyMem  Suprasorb | Mepilex® Border  Mepilex® Lite  Tegaderm™ Foam Adhesive  Allevyn Adhesive | Adaptic Touch®  Urgotul | Mepilex® XT Border Lite  Tegaderm™ Foam Adhesive | **1st Line: Honey**  Actilite  **2nd Line: Silver\***  Silvercel  Urgotul SSD  Suprasorb® X+PHMB | Mepilex®T Border xT  Tegaderm™ Foam Adhesive  Allevyn Adhesive |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| DuoDERM® Extra Thin |  | Tissue Type  PolyMem |  | PolyMem |  | DuoDERM® Extra Thin  PolyMem |  |  |  |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| AQUACEL® Extra™ Algivon | Tegaderm™ Foam Adhesive | Algivon  AQUACEL® Extra™  PolyMem  Suprasorb | Mepilex® Border  Tegaderm™ Foam Adhesive  Allevyn Adhesive | AQUACEL® Extra®  Sorbsan  PolyMem  Suprasorb | Mepilex® Border  Tegaderm™ Foam Adhesive  Allevyn Adhesive |  |  | **1st Line: Honey**  Algivon Plus  **2nd Line: Silver\***  Silvercel  Acticoat Flex 7  Suprasorb® X+PHMB | Mepilex®T Border xT  Tegaderm™ Foam Adhesive  Allevyn Adhesive |
| Algivon | Mepilex® XT Border  Allevyn Adhesive  Tegaderm™ Foam Adhesive  Eclypse | Algivon  AQUACEL® Extra™  PolyMem  Sorbasan Plus | Mepilex® Border  Tegaderm™ Foam Adhesive  Allevyn Adhesive  Eclypse | AQUACEL® Extra™  Sorbsan Plus  PolyMem | Mepilex® Border  Tegaderm™ Foam Adhesive  Allevyn Adhesive  Eclypse |  |  | **1st Line: Honey**  Algivon Plus  **2nd Line: Silver\***  Silvercel  Acticoat Flex 7  Suprasorb® X+PHMB | Mepilex®T Borde xTr  Tegaderm™ Foam Adhesive  Allevyn Adhesive |

High Exudate