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# BMJ Open

## A multi-centre, randomised controlled trial to compare the use of the Decellularised Dermis Allograft in addition to standard care versus standard care alone for the treatment of Venous Leg Ulceration – DAVE trial.

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3 1 **Title:** A multi-centre, randomised controlled trial to compare the use of the Decellularised Dermis  
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5 2 Allograft in addition to standard care versus standard care alone for the treatment of Venous Leg  
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7 3 Ulceration – DAVE trial.  
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9

10 52 **ABSTRACT**

11  
12 53 **Introduction:** Venous leg ulceration (VLU), the most common type of chronic ulcer, can be difficult to  
13  
14 54 heal and is a major cause of morbidity and reduced quality of life. Although compression bandaging is  
15  
16 55 the principal treatment, it is time consuming and bandage application requires specific training. There  
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18 56 is evidence that intervention on superficial venous incompetence can help ulcer healing and recurrence,  
19  
20 57 but this is not accessible to all patients. Hence, new treatments are required to address these chronic  
21  
22 58 wounds. One possible adjuvant treatment for VLU is human decellularised dermis (DCD), a type of skin  
23  
24 59 graft derived from skin from deceased tissue donors. Although DCD has the potential to promote ulcer  
25  
26 60 healing, there is a paucity of data for its use in patients with VLU.  
27

28 61 **Methods and analysis:** This is a multi-centre, parallel group, pragmatic randomised controlled trial.  
29  
30 62 One hundred and ninety-six patients with VLU will be randomly assigned to receive either the DCD  
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32 63 allograft in addition to standard care, or standard care alone. The primary outcome is the proportion of  
33  
34 64 participants with a healed index ulcer at 12-weeks post randomisation in each treatment arm.  
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36 65 Secondary outcomes include the time to index ulcer healing and the proportion of participants with a  
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38 66 healed index ulcer at 12-months. Changes in quality of life scores and cost-effectiveness will also be  
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40 67 assessed. All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic  
41  
42 68 regression on the outcome of the proportion of those with the index ulcer healed at 12-weeks, will be  
43  
44 69 performed. Secondary outcomes will be assessed using various statistical models appropriate to the  
45  
46 70 distribution and nature of these outcomes.  
47

48 71 **Ethics and dissemination:** Ethical approval was granted by the Bloomsbury Research Ethics  
49  
50 72 Committee (19/LO/1271). Findings will be published in a peer-reviewed journal and presented at  
51  
52 73 national and international conferences.  
53

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55 74 **Trial registration:** ISRCTN21541209.  
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57 75 **Keywords:** Venous leg ulceration, decellularised dermis allograft, compression bandaging  
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## ARTICLE SUMMARY

### Strengths and Limitations of the study

- To the authors' knowledge, this is the first randomised controlled trial evaluating the use of the decellularised dermis (DCD) allograft solely in patients with venous leg ulceration (VLU).
- The trial will follow up participants for 12-months, thus providing longer-term data on ulcer healing and recurrence.
- The data obtained from this study will support the development of VLU treatment and management strategies.
- The cost-effectiveness analysis will assess the economic impact of utilizing the DCD allograft for the management of patients with VLU, whose care consumes significant financial resource.
- The trial concentrates specifically on hard to heal ulcers, solely recruiting patients who have had an ulcer for at least 6-months.

**Word count: 3995**



## 107 INTRODUCTION

### 108 Background and rationale

109 Venous leg ulceration (VLU) describes a persistent wound in the lower limbs caused by a poorly  
110 functioning venous system. Characterised by chronicity and a protracted and intensive treatment, these  
111 wounds affect approximately 1-2% of the population, with prevalence increasing to up to 4% in those  
112 over 65 years of age (1,2).

113 Venous leg ulceration has a devastating impact on quality of life and social function especially in the  
114 elderly (3–5). The wounds can be very painful, resulting in reduced mobility, and require regular  
115 dressing changes, which can be extremely painful and time-consuming. Together, these factors result  
116 in negative quality of life effects as severe as those seen in other life limiting chronic conditions, such  
117 as congestive cardiac failure and chronic obstructive pulmonary disease (6).

118 Venous leg ulceration presents a significant burden to the healthcare service (7). Up to 50% of district  
119 nurse time is spent caring for people with chronic wounds, of which 70% will be venous in origin (8,9).  
120 Furthermore, ulcers can recur many times with up to 48% recurring at 5 years, thus requiring further  
121 treatment (10,11). Combined with the social cost due to loss of work and productivity, venous leg  
122 ulceration is estimated to cost up to 2% of the annual healthcare budget which equates to approximately  
123 £2.5 billion in the UK in 2017 (12). This is predicted to increase as a result of the ageing population  
124 (13).

125 The management of chronic VLU is therefore an important priority and public health concern.  
126 Compression, in the form of bandaging and stockings, is the underlying principle of treatment, with the  
127 aim of reducing venous hypertension (14). However, applying compression is time consuming; bandage  
128 application requires skill and stockings are not suitable for everyone (14,15). Furthermore, the reduction  
129 in community nursing numbers has resulted in increasing difficulty for patients to access this service  
130 (16,17).

131 Evidence from the ESCHAR and EVRA trials show that interventions to abolish superficial venous  
132 incompetence improve ulcer healing and recurrence (8,18). Although promising, such intervention is  
133 not accessible to all patients (19). Moreover, although EVRA reported that early intervention performed

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3 134 in ulcers with a duration of less than 6-months was beneficial, many patients present within leg  
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5 135 ulceration of greater duration than this, recurrent ulceration despite eradication of venous  
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7 136 incompetence, or may have underlying deep venous incompetence. These chronic wounds are known  
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9 137 to be hard to heal and require considerable nursing resources (10,20). The current treatments offered  
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11 138 are therefore insufficient for the management of VLU.

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14 139 Skin grafting represents an adjuvant treatment that can promote and expedite ulcer healing (21). Grafts  
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16 140 can be taken from the patient's own skin, from a donor or from tissue engineered skin (22). An autograft  
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18 141 (graft from own skin) can be performed in different ways, including pinch and punch grafting, mincing  
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20 142 and meshing (23). Despite promoting ulcer healing, drawbacks exist, including poor cosmetic outcomes  
21  
22 143 and the need for a formal surgical procedure in an operating theatre (24,25). Furthermore, surgical  
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24 144 waiting lists can be lengthy and, in the current NHS climate, bed availability is not guaranteed (26).  
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26 145 Thus, routine autografts are not accessible to all ulcer patients. Allografts (donor skin) and xenografts  
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28 146 (animal skin) have been successfully employed, but present similar drawbacks to autografts and the  
29  
30 147 potential for immunogenicity and disease transmission (27). Tissue engineered skin is donor skin that  
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32 148 has been processed to be made inert, and therefore is not immunogenic (28). A Cochrane review found  
33  
34 149 that tissue-engineered skin in conjunction with compression increased the healing rate in venous  
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36 150 ulceration; however, there was insufficient evidence to determine the effectiveness of any other skin  
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38 151 graft material (29).

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40 152 Human decellularised dermis (DCD) is generated from skin donations from deceased tissue donors  
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42 153 processed to remove epidermal and dermal cells while preserving dermal structures and is supplied  
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44 154 nationally by NHS Blood and Transplant [(NHSBT) (30,31)]. This provides an immunologically inert  
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46 155 scaffold to support cellular repopulation and tissue re-vascularisation. The advantage of the DCD  
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48 156 allograft is that it can be applied to the wound with local anaesthesia (via tissue staples or sutures) or  
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50 157 without (via tissue glue), and therefore does not require admission for a procedure under general  
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52 158 anaesthetic. The procedure can be performed in the outpatient department, avoiding inpatient  
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54 159 admission and theatre use, making the technique more accessible to a larger group of patients.

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56 160 The majority of DCD studies, including randomised controlled trials, have been performed in diabetic  
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58 161 populations (32–35). DCD allografts have been reported as safe, to promote angiogenesis (36) and, in

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3 162 randomised controlled trials, to significantly reduce ulcer healing time (by up to 50%), (37,38). Cohort  
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5 163 study data reveals a reduction in wound surface area, improved healing and volume in venous  
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7 164 ulceration, with evidence of angiogenesis, host cell migration and proliferation (39). This study  
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9 165 addresses the lack of robust research evidence about the effects of DCD allografts on VLU healing.

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12 166 This prospective, randomised, open (non-blinded), pragmatic trial will explore whether the DCD allograft  
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14 167 in addition to standard care, compared to standard care alone, will improve healing rates, reduce  
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16 168 recurrence, increase ulcer-free time and improve quality of life for those with VLU. In addition, a cost-  
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18 169 effectiveness analysis will be performed to assess the economic impact of utilizing the DCD allograft  
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20 170 for the management of this patient population, whose care consumes significant financial resource.

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22 171 Currently, the annual cost to manage VLU is approximately £1,200 per patient (14); however, in chronic  
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24 172 ulceration this is likely to be more. The NHS per patient costs for graft application will be approximately  
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26 173 £400. If a positive outcome results from this trial, the reduced ulcer healing time will likely result in  
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28 174 significantly reduced NHS costs with an improvement in quality adjusted life years (QALYs).

## 31 175 **Objectives**

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34 176 The primary objective is to determine whether the use of the DCD allograft in patients with VLU, in  
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36 177 addition to standard care, improves healing at 12-weeks compared to standard care alone. Secondary  
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38 178 objectives include comparisons of time to ulcer healing, change in ulcer area at 12-weeks, ulcer  
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40 179 recurrence at 12-months, quality of life (QoL) assessment at 12-weeks, 6-months and 12-months and  
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42 180 cost-effectiveness analysis.

## 45 182 **METHODS**

### 48 183 **Trial design**

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51 184 This is a prospective, randomised, open (non-blinded), pragmatic trial with a follow-up of 12 months.

### 54 185 **Study Setting**

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3 186 Eligible participants will be recruited from at least 10 sites in the United Kingdom. A full list of the study  
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5 187 sites can be found on the International Standard Randomised Controlled Trial Number (ISRCTN)  
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7 188 [registry \(ISRCTN21541209\)](https://www.isrctn.com/registry/index?search=ISRCTN21541209) (40).  
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### 10 189 **Eligibility Criteria**

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13 190 Inclusion criteria are: adult patients (> 18 years), able to provide informed consent with a diagnosis of  
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15 191 VLU with documented evidence of venous incompetence on duplex ultrasound, ulcer duration for > 6-  
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17 192 months and ulcer surface area  $\geq 2$  cm<sup>2</sup>. Exclusion criteria include: a diagnosis of sickle cell disease,  
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19 193 an ankle brachial pressure index (ABPI) < 0.8, a clinically infected ulcer, treatment with biomedical or  
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21 194 topical growth factors within the previous 30 days, a previous history of an inability to tolerate  
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23 195 compression therapy or a foot ulcer (i.e. below the ankle). The DCD allograft preparation entails the  
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25 196 use of a number of components, including specific antibiotics, which are then washed away. There  
26  
27 197 have been no documented allergic or hypersensitivity reactions to the DCD graft reported. Patients  
28  
29 198 with known allergies to the DCD preparation components are therefore able to participate at the  
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31 199 discretion of the clinical team.

### 32 200 **Interventions**

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35 201 All eligible patients will be informed about the study and provided with a written information sheet.  
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37 202 Consenting participants will be randomised to receive either the DCD allograft in addition to standard  
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39 203 care or standard care alone (Figure 1). Baseline demographic data will be collected for each participant,  
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41 204 including details of their past medical history and any concomitant medication. The EQ-5D (41) and  
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43 205 Charing Cross Venous Ulceration Questionnaire (CCVUQ) (42) will also be completed for generic and  
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45 206 disease-specific quality of life assessment respectively.

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48 207 Participants in the standard care arm will undergo wound cleaning and debridement, plus standard  
49  
50 208 compression therapy in the form of multilayer elastic compression bandaging or stockings. Participants  
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52 209 in the DCD arm will undergo wound cleaning and debridement and DCD allograft application. Following  
53  
54 210 application of the DCD allograft, a non-adhesive, non-absorbent, non-medicated primary dressing will  
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56 211 be applied, followed by the appropriate bolster/secondary dressings (31). Compression therapy will then  
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58 212 be applied in the form of multilayer elastic compression. Practice/district nurses will be advised not to  
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3 213 change the primary dressing the first 7-days post DCD allograft application. If the DCD allograft has not  
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5 214 adhered to the wound bed at the 1-week visit, the graft can be rinsed in saline (if it appears viable) and  
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7 215 reapplied and re-secured. Additional grafts will not be reapplied as part of the trial.  
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10 216 [Figure 1 about here]  
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13 217 As this is a pragmatic trial, the ulcer care in both arms will be as per local unit standard practice. All  
14  
15 218 participants will have their ulcers irrigated, cleaned and debrided according to best local practice.  
16  
17 219 Compression therapy will be according to local practice and may include multilayer elastic compression  
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19 220 bandaging or stockings designed to deliver between 20 to 40mm/Hg pressure. Wound dressing and  
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21 221 compression application will be performed by trained research nurses or community/district/practice  
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23 222 nurses as per standard care. The use of negative pressure wound therapy device will be left to the  
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25 223 discretion of the treating clinician. All participants may be offered interventional procedures in the form  
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27 224 of endovenous ablation (in the presence of superficial venous disease) dependent on whether local  
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29 225 recruitment site practice is to intervene upon ulcers over 6 months' duration. Once the wound has  
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31 226 healed, the participant will be given a minimum of Class II compression hosiery (18 – 24 mmHg) to wear  
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33 227 to prevent ulcer recurrence as per local practice. Endovenous ablation, amongst other procedures, at  
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35 228 any point post-randomisation, will be recorded at the 12-month follow-up.  
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### 37 229 **Primary outcome**

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40 230 The primary outcome is the proportion of participants with a healed index ulcer 12-weeks post  
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42 231 randomisation.  
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### 44 232 **Secondary outcomes**

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47 233 The secondary outcomes include:  
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- 50 234
- 51 • Time to index ulcer healing from randomisation
  - 52 235 • The percentage change in index ulcer area at 12-weeks from randomisation
  - 53 • The proportion of participants with a healed index ulcer at 12-months from randomisation
  - 54 236 • The proportion of those whose index ulcer healed for whom an ulcer recurred at the index site
  - 55 237 • The proportion of those whose index ulcer healed for whom an ulcer recurred at the index site
  - 56 238 within 12-months from randomisation
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3 239 • Change in QoL score at 12-weeks, 6-months and 12-months from randomisation using the EQ-  
4 240 5D and CCVUQ  
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7 241 • Cost-effectiveness analysis, measured using the Incremental Cost-Effectiveness Ratio (ICER)  
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10 242 **Sample Size and study duration**  
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13 243 To detect an absolute difference of 25% in the proportion of participants with a healed index ulcer at 12  
14 244 weeks (assuming a healing rate of 30% in the control group and 55% in the intervention group) and  
15 245 allowing for a 10% loss to follow up with a power of 90% and 5% level of significance, 196 patients are  
16 246 required (Stata/IC 15.1 for Mac, Statacorp, College Station, Texas, USA; procedure 'power twoprop',  
17 247 with continuity correction). The effect size was estimated from previously published literature on diabetic  
18 248 and venous ulceration, showing an absolute difference in the proportion of participants with a healed  
19 249 ulcer of 25% between intervention and control groups at 12 weeks (32,38,39). With the 12-month follow-  
20 250 up, this study will run for 36-months.  
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29 251 **Interim analysis**  
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31 252 When we have mature 12-week primary outcome data on the first 50 participants randomised, we will  
32 253 review the sample size with the independent TSC on the basis of recruitment rate, the overall (blinded)  
33 254 primary outcome of index ulcer healed proportion (expected to be  $(30+55/2) \approx 40\%$ ) and attrition rate  
34 255 (expected to be 10%).  
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40 256  
41 257 We plan on having a formal interim analysis with the possibility of stopping early for futility (no prospect  
42 258 of a clinically meaningful treatment effect, or for overwhelming evidence of effectiveness) at this point  
43 259 (of  $n=50$  with mature primary outcome data, or at around 25% of the total scheduled events observed).  
44  
45 260 This single interim analysis using a Lan-DeMets alpha spending approach with Fleming O'Brien  
46 261 boundaries has negligible effect on the required sample size (R 3.4.1 for Windows, package gsDesign).  
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51 262 **Recruitment**  
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54 263 Potential participants will be identified at outpatient clinic appointments. Posters and leaflets will also  
55 264 be displayed in the outpatient clinics and other appropriate locations.  
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59 265 Potentially eligible patients will receive a verbal explanation of the study and a patient information sheet  
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3 266 by the attending clinical/research team.  
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6 267 **Randomisation**  
7  
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9 268 Consent forms are completed on the day of treatment. Following confirmation of eligibility, consent and  
10 269 completion of baseline assessments, participants will then be randomly allocated to receive one of the  
11 270 two possible treatment options using an online computerised web system (REDCap, managed by the  
12 271 study data centre, University of Edinburgh). A minimization algorithm using centre, index ulcer size and  
13 272 duration will be used, including a random component to lessen predictability.  
14  
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19 273 **Blinding**  
20  
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22 274 As the DCD allograft is visible after application for a period of time, it is not possible to mask participants  
23 275 or the research/clinical teams to the treatment strategy. However the primary outcome assessments  
24 276 (verification of index ulcer healing visits) will be completed by an independent clinical assessor trained  
25 277 in the assessment of wound healing, who will have no previous involvement with, or knowledge of, the  
26 278 participant's index ulcer treatment and as such will be blind to the randomised treatment strategy (the  
27 279 DCD allograft is not expected to be visible after 4 weeks).  
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34

35 280 **Follow-up periods**  
36  
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38 281 All participants will attend for follow-up at 1-week, 3-weeks, 6-weeks and 12-weeks, 6-months, 9-  
39 282 months and 12-months post-randomisation. At all follow-up visits, a clinical assessment will be  
40 283 undertaken and a photograph and planimetry tracing of the ulcer will be collected (unless healing has  
41 284 been confirmed). The EQ-5D and the CCVUQ will be collected at baseline and the 12-week, 6- and 12-  
42 285 month follow-ups. Healthcare resource use will also be collected at 6- and 12-months.  
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48 286 Fortnightly calls will be made after the 6-week follow-up to check if the ulcer has healed. If the participant  
49 287 reports that their ulcer has healed, they will be invited to attend a verification visit, where a photograph  
50 288 of the ulcer will be taken. This photograph will be sent to an independent assessor (blinded to treatment  
51 289 allocation) for assessment and confirmation of healing status.  
52  
53  
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57 290 If the ulcer is confirmed as healed, monthly telephone calls will be performed to check for recurrence.

58 291 In the event that an ulcer is confirmed as healed, the recurrence, safety, resource use and health  
59  
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3 292 questionnaire data can be collected over the telephone or by post. If the participant fails to attend their  
4  
5 293 appointment, attempts will be made to collect the QoL and resource use questionnaires by telephone  
6  
7 294 or post. Participants will receive up to £10 for each visit attended as a contribution towards travel  
8  
9 295 expenses.

## 10 11 12 296 **Data collection and confidentiality**

13  
14  
15 297 Participant data will be stored in the password-protected REDCap database. Participant details will be  
16  
17 298 anonymised as each participant will be allocated a participant number. Identifiable data, including  
18  
19 299 contact information, will also be recorded on paper forms and will be kept in a locked filing cabinet in a  
20  
21 300 locked office at each investigational site. Data will be monitored for quality and completeness and  
22  
23 301 missing data will be requested from the participating sites, as per the data monitoring plan.

## 24 25 302 **ANALYSIS**

### 26 27 28 303 **Statistical analysis**

29  
30  
31 304 All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic regression  
32  
33 305 on the outcome of the proportion of those with the index ulcer healed at 12-weeks, with site as a random  
34  
35 306 effect and randomised group as the treatment effect, along with index ulcer size and duration at baseline  
36  
37 307 (the minimisation factors) and any other baseline factors known or suspected to be strongly related to  
38  
39 308 good or poor outcome, will form the model. Goodness of model fit will be examined using the Hosmer-  
40  
41 309 Lemeshow approach. The robustness of the findings to any patterns of missing data (both assuming  
42  
43 310 data are missing at random; and, if appropriate, informatively missing (missing not at random)) will be  
44  
45 311 explored using appropriate sensitivity analyses.

46  
47 312 Secondary outcomes (including the primary outcome at 12-months, time to index ulcer healing,  
48  
49 313 reduction in ulcer area at 12-weeks, ulcer recurrence at 12-months, and quality of life) will be assessed  
50  
51 314 using various statistical models appropriate to the distribution and nature of these outcomes, with the  
52  
53 315 same modelling strategy as per the primary outcome above (e.g. missing data and appropriate model  
54  
55 316 diagnostics).

56  
57 317 The proportion healed at 12-months and the recurrence of the index ulcer at 12-months will be analysed  
58  
59 318 as the primary outcome above. The time to index ulcer healing will be analysed using a survival type

60  
12



1  
2  
3 319 model (e.g. Cox proportional hazards model), and if the assumption regarding proportional hazards  
4  
5 320 fails, using a Restricted Mean Survival Time (RMST) approach. The reduction in area of the index ulcer  
6  
7 321 at 12 weeks over baseline will be analysed using a linear mixed model. The quality of life data (EQ-5D  
8  
9 322 and CCVUQ questionnaire) will be analysed using a repeated measures mixed linear models (with  
10  
11 323 repeated measures at 6-weeks, 6-months and 12-months and a suitable specified covariance  
12  
13 324 structure), with the overall treatment effect and the evolution of any treatment effect over time modelled.

### 15 325 **Cost-effectiveness analysis**

17  
18 326 A literature review will be conducted to identify other economic studies and other trials in comparable  
19  
20 327 populations. A within-trial analysis and a decision model will be constructed. In both cases, the main  
21  
22 328 analyses will be performed from the perspective of the NHS and Personal Social Services. Secondary  
23  
24 329 analyses will be performed from a societal perspective. The price year will be 2018-2019. Discounting  
25  
26 330 will be applied according to UK Government guidelines. The study will be reported according to  
27  
28 331 consolidated guidelines for economic evaluation (CHEERS) (43).

29  
30 332 The within-trial analysis will compare the treatment strategies within the 12-month time horizon of the  
31  
32 333 clinical trial on an ITT basis. Data will be collected by case note review and questionnaires completed  
33  
34 334 at baseline and follow-up.

35  
36 335 Resource use items in hospital and community care, adverse events or complications will be recorded  
37  
38 336 for each patient at 6- and 12-months. Resource use will be multiplied by UK unit costs obtained from  
39  
40 337 published literature, Healthcare Resource Groups, and manufacturers' list prices to calculate overall  
41  
42 338 costs. Utilities and QALYs will be calculated from the EQ-5D questionnaire. The extent of missing data  
43  
44 339 will be assessed and appropriate methods to handle missing data will be applied.

45  
46 340 The decision model provides a framework to incorporate evidence from other relevant studies and to  
47  
48 341 extrapolate outcomes, such as ulcer healing and recurrence, beyond the trial reporting period. The  
49  
50 342 Markov model will include the key ulcer-related health states and events that may occur during the  
51  
52 343 lifetime of the patient. The data to support extrapolation may be taken from the trial (e.g. fitting  
53  
54 344 parametric time-to-event functions to the trial data) or may come from external sources (such as the  
55  
56 345 literature review or observational data)(44,45).

1  
2  
3 346 In both the within trial and model analyses, the incremental cost-effectiveness ratio will be calculated  
4  
5 347 and compared to current UK decision making thresholds. Sensitivity analysis will be carried out to test  
6  
7 348 the robustness of results to alternative assumptions about model structure or data. The cost-  
8  
9 349 effectiveness acceptability curve will be calculated using probabilistic sensitivity analysis (43).

#### 10 11 350 **Data monitoring, safety and quality control**

12  
13 351 An independent Trial Steering Committee (TSC) and independent Data Monitoring Committee (iDMC)  
14  
15 352 have been appointed. The main role of the TSC is to provide overall supervision of the trial and ensure  
16  
17 353 that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the  
18  
19 354 relevant regulations, whilst the main role of the iDMC is to safeguard the interests of trial participants  
20  
21 355 and to monitor the main outcome measures including safety and efficacy. A clinical trial manager,  
22  
23 356 together with the Trial Management Group (TMG), will oversee trial progress.

24  
25 357 All treatment related adverse events (AEs; related to the skin graft or leg ulcer only) will be collected as  
26  
27 358 will all serious adverse events (SAEs). The chief investigator (CI) will be notified of all SAEs within 24  
28  
29 359 hours. All SAEs will be reported to the research ethics committee (REC) if, in the opinion of the CI, the  
30  
31 360 event was related to the intervention. All related AEs and SAEs will be recorded and summarised by  
32  
33 361 treatment strategy. These analyses will be descriptive, with any p-values calculated to be interpreted  
34  
35 362 descriptively.

#### 36 37 363 **DISCUSSION**

38  
39  
40 364 Although compression therapy is the mainstay of treatment, there is a need to explore new treatments  
41  
42 365 for wounds that are chronic and persistent in nature. This is the first randomised controlled trial to  
43  
44 366 evaluate the use of DCD allograft for the treatment of VLU. This study will provide important data on  
45  
46 367 whether the use of the DCD allograft plus standard care is associated with improved outcomes  
47  
48 368 compared to standard care alone and will provide important data on its effects on quality of life and  
49  
50 369 healthcare costs.

#### 51 52 370 **Patient and public involvement**

53  
54 371 Focus groups were held with patients accessing the vascular clinic at Imperial College Healthcare NHS  
55  
56 372 Trust to obtain views on the proposed study and the acceptability of the DCD allograft. The focus group  
57  
58 373 helped to inform important aspects of the trial, including the number of visits and questionnaires used  
59  
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1  
2  
3 374 in the study. A Patient and Public Involvement (PPI) representative was included as a co-applicant and  
4  
5 375 provided invaluable input in the study design. A PPI representative also sits on the TSC, providing real  
6  
7 376 time input on study progress. He will also aid with dissemination of the results.  
8  
9

### 10 377 **Ethics approval and consent to participate**

11  
12 378 Ethical approval was granted by the Bloomsbury Research Ethics Committee (19/LO/1271).  
13  
14 379 Amendments to the protocol will be updated on the ISRCTN record. All amendments to the protocol will  
15  
16 380 be submitted to the sponsor for review before applying for approval from the REC and the Health  
17  
18 381 Research Authority (HRA). Standard informed consent will be taken with freedom to withdraw at any  
19  
20 382 time.  
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### 23 383 **Publication of data**

24  
25  
26 384 The findings from this study will be published in a peer-reviewed journal and presented at national and  
27  
28 385 international conferences.  
29

30  
31 386 **Current study status:** The current version of the protocol is v8.0. The study commenced recruitment  
32  
33 387 in October 2019.  
34

### 35 388 **Trial sponsor**

36  
37 389 Imperial College London is the main sponsor for this study. Delegated responsibilities are assigned to  
38  
39 390 the NHS trusts taking part in this study.  
40  
41 391

42  
43 392 **Funding statement:** This study is supported by the J P Moulton Charitable Foundation. The DCD  
44  
45 393 allograft is provided free of charge by NHSBT. The design, management, analysis and reporting of the  
46  
47 394 study are entirely independent of J P Moulton Charitable Foundation and NHSBT.  
48

### 49 395 **Availability of data and materials**

50  
51 396 Not applicable  
52  
53 397

### 54 55 398 **Author contributions**

1  
2  
3 399 AHD, SO, TL, FH and LB were involved in the design of the study and securing funding. AHD, SO and  
4  
5 400 FH drafted the protocol and applied for ethical approval. AHD and SO supervise the project. FH and  
6  
7 401 SP coordinate the project. SO, AHD and SP drafted the manuscript. JN and RL will conduct the  
8  
9 402 statistical analysis. DE will conduct the cost-effectiveness analysis. All authors have read and approved  
10  
11 403 the final manuscript. AHD acts as guarantor.

#### 12 13 14 404 **Competing interests**

15  
16 405 AC and RL are affiliated to NHS Blood and Transplant (NHSBT), who are providing the DCD  
17  
18 406 allografts free of charge. There are no other conflicts of interest to declare.

#### 19 20 21 407 **Abbreviations**

22  
23  
24 408 ABPI: Ankle Brachial Pressure Index; AE: Adverse Event; CI: Chief Investigator; CCVUQ: Charing  
25  
26 409 Cross Venous Ulcer Questionnaire; CRN: Clinical Research Network; CHEERS: Consolidated Health  
27  
28 410 Economic Evaluation Reporting Standards; DCD: Decellularised dermis; EQ-5D: EuroQol Five-  
29  
30 411 Dimension; GP: General Practitioner; GCP: Good Clinical Practice; HRA: Health Research Authority;  
31  
32 412 ICER: Incremental Cost-Effectiveness Ratio; iDMC: Independent Data Monitoring Committee; ITT:  
33  
34 413 Intention-to-treat; ISRCTN: International Standard Randomised Controlled Trial Number; NHSBT:  
35  
36 414 National Health Service Blood and Transplant; NIHR: National Institute for Health Research; Patient  
37  
38 415 and Public Involvement: PPI; REDCap: Research Electronic Data Capture; REC: Research Ethics  
39  
40 416 Committee; RMST: Restricted Mean Survival Time; TMG: Trial Management Group; TSC: Trial Steering  
41  
42 417 Committee; QALY: Quality-adjusted life year; QoL: Quality of Life; Venous leg ulceration: VLU.

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51  
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53  
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55  
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57  
58 424 helped to inform the design of the study.

425

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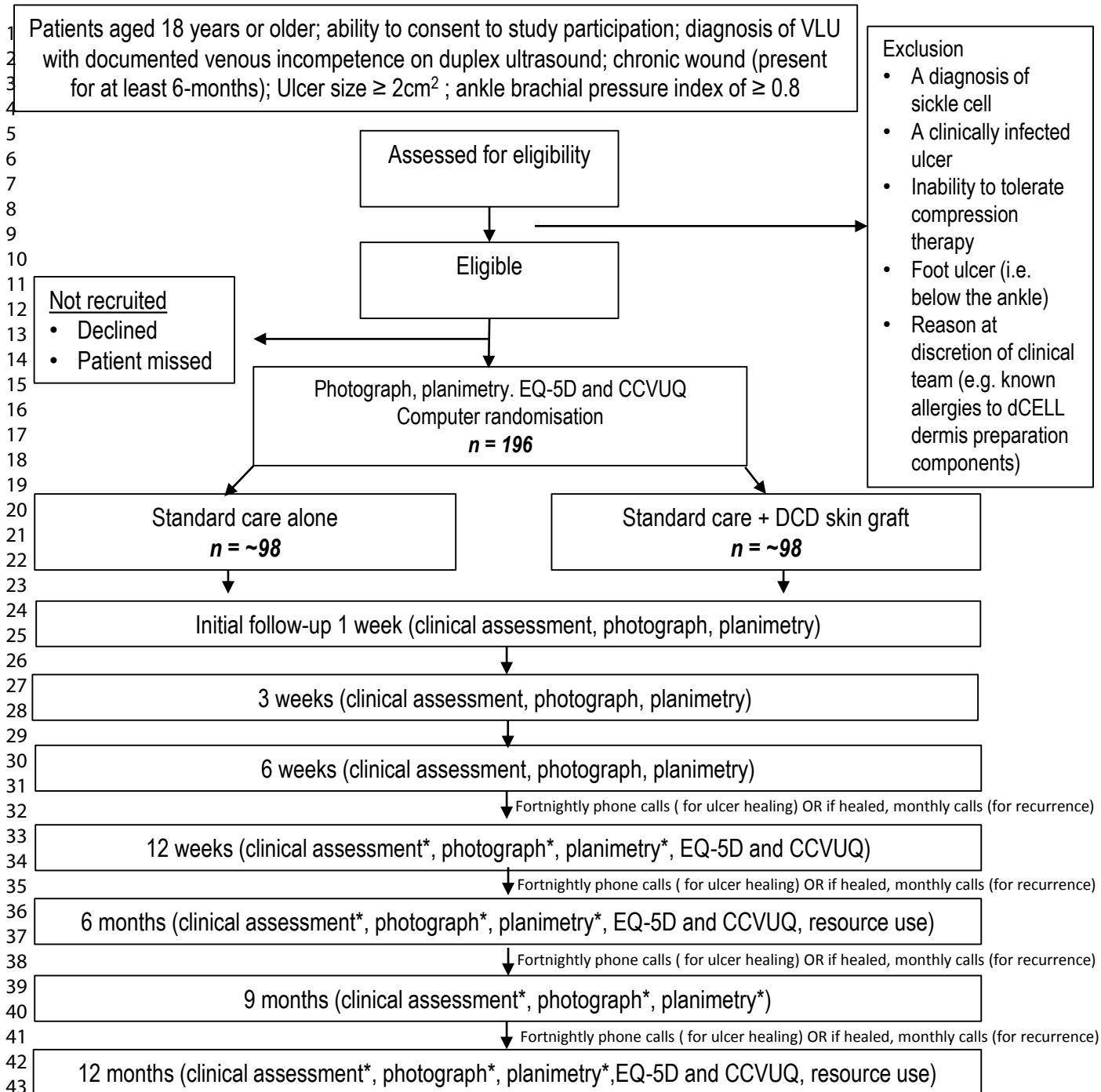


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# Evaluation of decellularised dermis allograft for the treatment of venous leg ulceration





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____ 1 _____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____ 3 _____
	2b	All items from the World Health Organization Trial Registration Data Set	Included in trial registry and throughout manuscript
Protocol version	3	Date and version identifier	_____ 15 _____
Funding	4	Sources and types of financial, material, and other support	_____ 15 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1-2 _____
	5b	Name and contact information for the trial sponsor	_____ 15 _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____ 15 _____

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1	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____ 14 _____
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10	<b>Introduction</b>		
11	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant
12	rationale		studies (published and unpublished) examining benefits and harms for each intervention
13			_____ 5-7 _____
14		6b	Explanation for choice of comparators
15			_____ 5-7 _____
16	Objectives	7	Specific objectives or hypotheses
17			_____ 7 _____
18	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
19			_____ 7 _____
20			
21			
22	<b>Methods: Participants, interventions, and outcomes</b>		
23			
24	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
25			_____ 8 _____
26			
27	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
28			_____ 8 _____
29			
30	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
31			_____ 8-9 _____
32		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
33			_____ 10, 12 _____
34		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
35			_____ N/A _____
36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
37			_____ 9 _____
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1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
6	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-12
9	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

19	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
25	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
33	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
36		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

**Methods: Data collection, management, and analysis**

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1	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	_8,12_
2	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of	
3			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	
4			Reference to where data collection forms can be found, if not in the protocol	
5				
6		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	___11-12___
7			collected for participants who discontinue or deviate from intervention protocols	
8				
9	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	___12___
10			(eg, double data entry; range checks for data values). Reference to where details of data management	
11			procedures can be found, if not in the protocol	
12				
13				
14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	___12-13___
15			statistical analysis plan can be found, if not in the protocol	
16				
17		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___10, 13-14_
18				
19		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	
20			statistical methods to handle missing data (eg, multiple imputation)	___12___
21				
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23	<b>Methods: Monitoring</b>			
24				
25	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	___14___
26			whether it is independent from the sponsor and competing interests; and reference to where further details	
27			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
28			needed	
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31		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	___10_
32			results and make the final decision to terminate the trial	
33				
34	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	___14___
35			events and other unintended effects of trial interventions or trial conduct	
36				
37	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	___N/A___
38			from investigators and the sponsor	
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41	<b>Ethics and dissemination</b>			
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1	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 15 ___
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4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 15 ___
5				
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8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___ 10-11 ___
9				
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12		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___ N/A ___
13				
14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	___ 12 ___
15				
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18	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___ 16 ___
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21	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ N/A ___
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24	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___ N/A ___
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27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___ N/A ___
28				
29		31b	Authorship eligibility guidelines and any intended use of professional writers	___ N/A ___
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31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___ N/A ___
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36	<b>Appendices</b>			
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38	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___ Provided on request ___
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1	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	___N/A___
2	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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# BMJ Open

## A study protocol for a multi-centre, randomised controlled trial to compare the use of the Decellularised Dermis Allograft in addition to standard care versus standard care alone for the treatment of Venous Leg Ulceration – DAVE trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041748.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Jan-2021
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<b>Primary Subject Heading</b>:	Cardiovascular medicine

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Secondary Subject Heading:	Nursing
Keywords:	VASCULAR MEDICINE, WOUND MANAGEMENT, Vascular surgery < SURGERY





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3 1 **Title:** A study protocol for a multi-centre, randomised controlled trial to compare the use of the  
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10 52 **ABSTRACT**

11  
12 53 **Introduction:** Venous leg ulceration (VLU), the most common type of chronic ulcer, can be difficult to  
13  
14 54 heal and is a major cause of morbidity and reduced quality of life. Although compression bandaging is  
15  
16 55 the principal treatment, it is time consuming and bandage application requires specific training. There  
17  
18 56 is evidence that intervention on superficial venous incompetence can help ulcer healing and recurrence,  
19  
20 57 but this is not accessible to all patients. Hence, new treatments are required to address these chronic  
21  
22 58 wounds. One possible adjuvant treatment for VLU is human decellularised dermis (DCD), a type of skin  
23  
24 59 graft derived from skin from deceased tissue donors. Although DCD has the potential to promote ulcer  
25  
26 60 healing, there is a paucity of data for its use in patients with VLU.

27  
28 61 **Methods and analysis:** This is a multi-centre, parallel group, pragmatic randomised controlled trial.  
29  
30 62 One hundred and ninety-six patients with VLU will be randomly assigned to receive either the DCD  
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32 63 allograft in addition to standard care, or standard care alone. The primary outcome is the proportion of  
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34 64 participants with a healed index ulcer at 12-weeks post randomisation in each treatment arm.  
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36 65 Secondary outcomes include the time to index ulcer healing and the proportion of participants with a  
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38 66 healed index ulcer at 12-months. Changes in quality of life scores and cost-effectiveness will also be  
39  
40 67 assessed. All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic  
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42 68 regression on the outcome of the proportion of those with the index ulcer healed at 12-weeks, will be  
43  
44 69 performed. Secondary outcomes will be assessed using various statistical models appropriate to the  
45  
46 70 distribution and nature of these outcomes.

47  
48 71 **Ethics and dissemination:** Ethical approval was granted by the Bloomsbury Research Ethics  
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50 72 Committee (19/LO/1271). Findings will be published in a peer-reviewed journal and presented at  
51  
52 73 national and international conferences.

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55 74 **Trial registration:** ISRCTN21541209.

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57 75 **Keywords:** Venous leg ulceration, decellularised dermis allograft, compression bandaging  
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**77 ARTICLE SUMMARY****78 Strengths and Limitations of the study**

- 79 - To the authors' knowledge, this is the first randomised controlled trial evaluating the use of the
- 80 decellularised dermis (DCD) allograft solely in patients with venous leg ulceration (VLU).
- 81 - The trial will follow up participants for 12-months, thus providing longer-term data on ulcer
- 82 healing and recurrence.
- 83 - The cost-effectiveness analysis will assess the economic impact of utilizing the DCD allograft
- 84 for the management of patients with VLU, whose care consumes significant financial resource.
- 85 - The trial concentrates specifically on hard to heal ulcers, solely recruiting patients who have
- 86 had an ulcer for at least 6-months.

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**88 Word count: 4034**

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**105 INTRODUCTION**



## 106 **Background and rationale**

107 Venous leg ulceration (VLU) describes a persistent wound in the lower limbs caused by a poorly  
108 functioning venous system. Characterised by chronicity and a protracted and intensive treatment, these  
109 wounds affect approximately 1-2% of the population, with prevalence increasing to up to 4% in those  
110 over 65 years of age (1,2).

111 Venous leg ulceration has a devastating impact on quality of life and social function especially in the  
112 elderly (3–5). The wounds can be very painful, resulting in reduced mobility, and require regular  
113 dressing changes, which can be extremely painful and time-consuming. Together, these factors result  
114 in negative quality of life effects as severe as those seen in other life limiting chronic conditions, such  
115 as congestive cardiac failure and chronic obstructive pulmonary disease (6).

116 Venous leg ulceration presents a significant burden to the healthcare service (7). Up to 50% of district  
117 nurse time is spent caring for people with chronic wounds, of which 70% will be venous in origin (8,9).  
118 Furthermore, ulcers can recur many times with up to 48% recurring at 5 years, thus requiring further  
119 treatment (10,11). Combined with the social cost due to loss of work and productivity, venous leg  
120 ulceration is estimated to cost up to 2% of the annual healthcare budget which equates to approximately  
121 £2.5 billion in the UK in 2017 (12). This is predicted to increase as a result of the ageing population  
122 (13).

123 The management of chronic VLU is therefore an important priority and public health concern.  
124 Compression, in the form of bandaging and stockings, is the underlying principle of treatment, with the  
125 aim of reducing venous hypertension (14). However, applying compression is time consuming; bandage  
126 application requires skill and stockings are not suitable for everyone (14,15). Furthermore, the reduction  
127 in community nursing numbers has resulted in increasing difficulty for patients to access this service  
128 (16,17).

129 Evidence from the ESCHAR and EVRA trials show that interventions to abolish superficial venous  
130 incompetence improve ulcer healing and recurrence (8,18). Although promising, such intervention is  
131 not accessible to all patients (19). Moreover, although EVRA reported that early intervention performed  
132 in ulcers with a duration of less than 6-months was beneficial, many patients present within leg

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3 133 ulceration of greater duration than this, recurrent ulceration despite eradication of venous  
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5 134 incompetence, or may have underlying deep venous incompetence. These chronic wounds are known  
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7 135 to be hard to heal and require considerable nursing resources (10,20). The current treatments offered  
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9 136 are therefore insufficient for the management of VLU.

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11  
12 137 Skin grafting represents an adjuvant treatment that can promote and expedite ulcer healing (21). Grafts  
13  
14 138 can be taken from the patient's own skin, from a donor or from tissue engineered skin (22). An autograft  
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16 139 (graft from own skin) can be performed in different ways, including pinch and punch grafting, mincing  
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18 140 and meshing (23). Despite promoting ulcer healing, drawbacks exist, including poor cosmetic outcomes  
19  
20 141 and the need for a formal surgical procedure in an operating theatre in some instances (24,25).  
21  
22 142 Furthermore, surgical waiting lists can be lengthy and, in the current NHS climate, bed availability is not  
23  
24 143 guaranteed (26). Thus, routine autografts are not accessible to all ulcer patients. Allografts (donor skin)  
25  
26 144 and xenografts (animal skin) have been successfully employed, but present similar drawbacks to  
27  
28 145 autografts and the potential for immunogenicity and disease transmission (27). Tissue engineered skin  
29  
30 146 is donor skin that has been processed to be made inert, and therefore is not immunogenic (28). A  
31  
32 147 Cochrane review found that tissue-engineered skin in conjunction with compression increased the  
33  
34 148 healing rate in venous ulceration; however, there was insufficient evidence to determine the  
35  
36 149 effectiveness of any other skin graft material (29).

37  
38 150 Human decellularised dermis (DCD) is generated from skin donations from deceased tissue donors  
39  
40 151 processed to remove epidermal and dermal cells while preserving dermal structures and is supplied  
41  
42 152 nationally by NHS Blood and Transplant [(NHSBT) (30,31)]. This provides an immunologically inert  
43  
44 153 scaffold to support cellular repopulation and tissue re-vascularisation. Although allografts can only serve  
45  
46 154 as temporary cover, the advantage of the DCD allograft is that it can be applied to the wound with local  
47  
48 155 anaesthesia (via tissue staples or sutures) or without (via tissue glue), and therefore does not require  
49  
50 156 admission for a procedure under general anaesthetic. The procedure can be performed in the outpatient  
51  
52 157 department, avoiding inpatient admission and theatre use, making the technique more accessible to a  
53  
54 158 larger group of patients.

55  
56 159 The majority of DCD studies, including randomised controlled trials, have been performed in diabetic  
57  
58 160 populations (32–35). DCD allografts have been reported as safe, to promote angiogenesis (36) and, in

1  
2  
3 161 randomised controlled trials, to significantly reduce ulcer healing time (by up to 50%), (37,38). Cohort  
4  
5 162 study data reveals a reduction in wound surface area, improved healing and volume in venous  
6  
7 163 ulceration, with evidence of angiogenesis, host cell migration and proliferation (39). This study  
8  
9 164 addresses the lack of robust research evidence about the effects of DCD allografts on VLU healing.

10  
11  
12 165 This prospective, randomised, open (non-blinded), pragmatic trial will explore whether the DCD allograft  
13  
14 166 in addition to standard care, compared to standard care alone, will improve healing rates, reduce  
15  
16 167 recurrence, increase ulcer-free time and improve quality of life for those with VLU. In addition, a cost-  
17  
18 168 effectiveness analysis will be performed to assess the economic impact of utilizing the DCD allograft  
19  
20 169 for the management of this patient population, whose care consumes significant financial resource.

21  
22 170 Currently, the annual cost to conservatively manage VLU is approximately £1,200 per patient (14);  
23  
24 171 however, in chronic ulceration this is likely to be more. The NHS per patient costs for graft application  
25  
26 172 will be approximately £400. If a positive outcome results from this trial, the reduced ulcer healing time  
27  
28 173 will likely result in significantly reduced NHS costs with an improvement in quality adjusted life years  
29  
30 174 (QALYs).

### 31 32 33 175 **Objectives**

34  
35  
36 176 The primary objective is to determine whether the use of the DCD allograft in patients with VLU, in  
37  
38 177 addition to standard care, improves healing at 12-weeks compared to standard care alone. Secondary  
39  
40 178 objectives include comparisons of time to ulcer healing, change in ulcer area at 12-weeks, ulcer  
41  
42 179 recurrence at 12-months, quality of life (QoL) assessment at 12-weeks, 6-months and 12-months and  
43  
44 180 cost-effectiveness analysis.

45  
46 181

### 47 182 **METHODS AND ANALYSIS**

#### 48 49 50 183 **Trial design**

51  
52  
53 184 This is a prospective, randomised, open (non-blinded), pragmatic trial with a follow-up of 12 months.

#### 54 55 56 185 **Study Setting**

1  
2  
3 186 Eligible participants will be recruited from at least 10 sites in the United Kingdom. A full list of the study  
4  
5 187 sites can be found on the International Standard Randomised Controlled Trial Number (ISRCTN)  
6  
7 188 [registry \(ISRCTN21541209\)](https://www.isrctn.com/ISRCTN21541209) (40).  
8  
9

### 10 189 **Eligibility Criteria**

11  
12  
13 190 Inclusion criteria are: adult patients (> 18 years), able to provide informed consent with a diagnosis of  
14  
15 191 VLU with documented evidence of venous incompetence on duplex ultrasound, ulcer duration for > 6-  
16  
17 192 months and ulcer surface area  $\geq 2$  cm<sup>2</sup>. Exclusion criteria include: a diagnosis of sickle cell disease,  
18  
19 193 an ankle brachial pressure index (ABPI) < 0.8, a clinically infected ulcer, treatment with biomedical or  
20  
21 194 topical growth factors within the previous 30 days, a previous history of an inability to tolerate  
22  
23 195 compression therapy or a foot ulcer (i.e. below the ankle). The DCD allograft preparation entails the  
24  
25 196 use of a number of components, including specific antibiotics, which are then washed away. There  
26  
27 197 have been no documented allergic or hypersensitivity reactions to the DCD graft reported. Patients  
28  
29 198 with known allergies to the DCD preparation components are therefore able to participate at the  
30  
31 199 discretion of the clinical team.

### 32 200 **Interventions**

33  
34  
35 201 All eligible patients will be informed about the study and provided with a written information sheet.  
36  
37 202 Consenting participants will be randomised to receive either the DCD allograft in addition to standard  
38  
39 203 care or standard care alone (Figure 1). Baseline demographic data will be collected for each participant,  
40  
41 204 including details of their past medical history and any concomitant medication. The EQ-5D (41) and  
42  
43 205 Charing Cross Venous Ulceration Questionnaire (CCVUQ) (42) will also be completed for generic and  
44  
45 206 disease-specific quality of life assessment respectively.

46  
47  
48 207 Participants in the standard care arm will undergo wound cleaning and debridement, plus standard  
49  
50 208 compression therapy in the form of multilayer elastic compression bandaging or stockings. Participants  
51  
52 209 in the DCD arm will undergo wound cleaning and debridement and DCD allograft application. The DCD  
53  
54 210 graft will be applied by trained registered healthcare professionals (physicians or nurses). Training on  
55  
56 211 the application of the DCD graft will be provided by NHSBT. The DCD will be applied to the debrided  
57  
58 212 index ulcer wound bed. Recommendations will be made that the DCD should be secured with surgical  
59  
60

1  
2  
3 213 glue, staples and/or sutures to optimise graft adhesion. The DCD graft should be fenestrated liberally  
4  
5 214 with a scalpel or scissors to allow wound exudate to pass through to reduce risk of seroma/haematoma  
6  
7 215 developing under DCD. Following application of the DCD allograft, a non-adhesive, non-absorbent,  
8  
9 216 non-medicated primary dressing will be applied, followed by the appropriate bolster/secondary  
10  
11 217 dressings (31). Compression therapy will then be applied in the form of multilayer elastic compression.  
12  
13 218 Practice/district nurses will be advised not to change the primary dressing the first 7-days post DCD  
14  
15 219 allograft application. If the DCD allograft has not adhered to the wound bed at the 1-week visit, the graft  
16  
17 220 can be rinsed in saline (if it appears viable) and reapplied and re-secured. Additional grafts will not be  
18  
19 221 reapplied as part of the trial.

20  
21  
22 222

22 223 [Figure 1 about here]

24  
25 224 As this is a pragmatic trial, the ulcer care in both arms will be as per local unit standard practice. All  
26  
27 225 participants will have their ulcers irrigated, cleaned and debrided according to best local practice.  
28  
29 226 Compression therapy will be according to local practice and may include multilayer elastic compression  
30  
31 227 bandaging or stockings designed to deliver between 20 to 40mm/Hg pressure. Wound dressing and  
32  
33 228 compression application will be performed by trained research nurses or community/district/practice  
34  
35 229 nurses as per standard care. In the event of a missed visit, local study teams will liaise with/ask the  
36  
37 230 participant to liaise with the district/community/practice nurse to arrange dressing change and  
38  
39 231 compression application. The use of negative pressure wound therapy device will be left to the  
40  
41 232 discretion of the treating clinician. All participants may be offered interventional procedures in the form  
42  
43 233 of endovenous ablation (in the presence of superficial venous disease) dependent on whether local  
44  
45 234 recruitment site practice is to intervene upon ulcers over 6 months' duration. Once the wound has  
46  
47 235 healed, the participant will be given a minimum of Class II compression hosiery (18 – 24 mmHg) to wear  
48  
49 236 to prevent ulcer recurrence as per local practice. Endovenous ablation, amongst other procedures, at  
50  
51 237 any point post-randomisation, will be recorded at the 12-month follow-up.

52  
53 238 **Primary outcome**

54  
55  
56 239 The primary outcome is the proportion of participants with a healed index ulcer 12-weeks post  
57  
58 240 randomisation.

## 241 **Secondary outcomes**

242 The secondary outcomes include:

- 243 • Time to index ulcer healing from randomisation
- 244 • The percentage change in index ulcer area at 12-weeks from randomisation
- 245 • The proportion of participants with a healed index ulcer at 12-months from randomisation
- 246 • The proportion of those whose index ulcer healed for whom an ulcer recurred at the index site  
247 within 12-months from randomisation
- 248 • Change in QoL score at 12-weeks, 6-months and 12-months from randomisation using the EQ-  
249 5D and CCVUQ
- 250 • Cost-effectiveness analysis, measured using the Incremental Cost-Effectiveness Ratio (ICER)

## 251 **Sample Size and study duration**

252 To detect an absolute difference of 25% in the proportion of participants with a healed index ulcer at 12  
253 weeks (assuming a healing rate of 30% in the control group and 55% in the intervention group) and  
254 allowing for a 10% loss to follow up with a power of 90% and 5% level of significance, 196 patients are  
255 required (Stata/IC 15.1 for Mac, Statacorp, College Station, Texas, USA; procedure 'power twoprop',  
256 with continuity correction). The effect size was estimated from previously published literature on diabetic  
257 and venous ulceration, showing an absolute difference in the proportion of participants with a healed  
258 ulcer of 25% between intervention and control groups at 12 weeks (32,38,39). With the 12-month follow-  
259 up, this study will run for 36-months.

## 260 **Interim analysis**

261 When we have mature 12-week primary outcome data on the first 50 participants randomised, we will  
262 review the sample size with the independent TSC on the basis of recruitment rate, the overall (blinded)  
263 primary outcome of index ulcer healed proportion (expected to be  $(30+55/2) \approx 40\%$ ) and attrition rate  
264 (expected to be 10%).

265

266 We plan on having a formal interim analysis with the possibility of stopping early for futility (no prospect  
267 of a clinically meaningful treatment effect, or for overwhelming evidence of effectiveness) at this point

1  
2  
3 268 (of n=50 with mature primary outcome data, or at around 25% of the total scheduled events observed).  
4  
5 269 This single interim analysis using a Lan-DeMets alpha spending approach with Fleming O'Brien  
6  
7 270 boundaries has negligible effect on the required sample size (R 3.4.1 for Windows, package gsDesign).  
8  
9

### 10 271 **Recruitment**

11  
12  
13 272 Potential participants will be identified at outpatient clinic appointments. Posters and leaflets will also  
14  
15 273 be displayed in the outpatient clinics and other appropriate locations.

16  
17  
18 274 Potentially eligible patients will receive a verbal explanation of the study and a patient information sheet  
19  
20 275 by the attending clinical/research team.

### 21 22 276 **Randomisation**

23  
24  
25 277 Consent forms are completed on the day of treatment. Following confirmation of eligibility, consent and  
26  
27 278 completion of baseline assessments, participants will then be randomly allocated to receive one of the  
28  
29 279 two possible treatment options using an online computerised web system (REDCap, managed by the  
30  
31 280 study data centre, University of Edinburgh). A minimization algorithm using centre, index ulcer size and  
32  
33 281 duration will be used, including a random component to lessen predictability.

### 34 35 36 282 **Blinding**

37  
38  
39 283 As the DCD allograft is visible after application for a period of time, it is not possible to mask participants  
40  
41 284 or the research/clinical teams to the treatment strategy. However the primary outcome assessments  
42  
43 285 (verification of index ulcer healing visits) will be completed by an independent clinical assessor trained  
44  
45 286 in the assessment of wound healing, who will have no previous involvement with, or knowledge of, the  
46  
47 287 participant's index ulcer treatment and as such will be blind to the randomised treatment strategy (the  
48  
49 288 DCD allograft is not expected to be visible after 4 weeks).

### 50 51 289 **Follow-up periods**

52  
53  
54 290 All participants will attend for follow-up at 1-week, 3-weeks, 6-weeks and 12-weeks, 6-months, 9-  
55  
56 291 months and 12-months post-randomisation. At all follow-up visits, a clinical assessment will be  
57  
58 292 undertaken and a photograph and planimetry tracing of the ulcer will be collected (unless healing has  
59  
60



1  
2  
3 293 been confirmed). The EQ-5D and the CCVUQ will be collected at baseline and the 12-week, 6- and 12-  
4  
5 294 month follow-ups. Healthcare resource use (procedures, hospital, GP and community nurse visits,  
6  
7 295 physiotherapy and other interventions), days lost from work and normal activities, carer time and out-  
8  
9 296 of-pocket expenses related to leg ulcer care will also be collected from case notes and patient diaries  
10  
11 297 during the initial procedure and at 6- and 12-months.

12  
13  
14 298 Fortnightly calls will be made after the 6-week follow-up to check if the ulcer has healed. If the  
15  
16 299 participant reports that their ulcer has healed, they will be invited to attend a verification visit, where a  
17  
18 300 photograph of the ulcer will be taken. This photograph will be sent to an independent assessor  
19  
20 301 (blinded to treatment allocation) for assessment and confirmation of healing status. Ulcer healing is  
21  
22 302 defined as complete re-epithelialisation of the index ulcer in the absence of a scab (eschar) with no  
23  
24 303 dressing required confirmed by blinded photo assessment of healing.

25  
26 304 If the ulcer is confirmed as healed, monthly telephone calls will be performed to check for recurrence.  
27  
28 305 In the event that an ulcer is confirmed as healed, the recurrence, safety, resource use and health  
29  
30 306 questionnaire data can be collected over the telephone or by post. If the participant fails to attend their  
31  
32 307 appointment, attempts will be made to collect the QoL and patient resource use diaries by telephone or  
33  
34 308 post. Participants will receive up to £10 for each visit attended as a contribution towards travel  
35  
36 309 expenses.

### 37 38 39 310 **Data collection and confidentiality**

40  
41 311 Participant data will be stored in the password-protected REDCap database. Participant details will be  
42  
43 312 anonymised as each participant will be allocated a participant number. Identifiable data, including  
44  
45 313 contact information, will also be recorded on paper forms and will be kept in a locked filing cabinet in a  
46  
47 314 locked office at each investigational site. Data will be monitored for quality and completeness and  
48  
49 315 missing data will be requested from the participating sites, as per the data monitoring plan.

### 50 51 52 316 **Statistical analysis**

53  
54  
55 317 All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic regression  
56  
57 318 on the outcome of the proportion of those with the index ulcer healed at 12-weeks, with site as a random  
58  
59 319 effect and randomised group as the treatment effect, along with index ulcer size and duration at baseline



1  
2  
3 320 (the minimisation factors) and any other baseline factors known or suspected to be strongly related to  
4  
5 321 good or poor outcome, will form the model. Goodness of model fit will be examined using the Hosmer-  
6  
7 322 Lemeshow approach. The robustness of the findings to any patterns of missing data (both assuming  
8  
9 323 data are missing at random; and, if appropriate, informatively missing (missing not at random)) will be  
10  
11 324 explored using appropriate sensitivity analyses.

12  
13 325 Secondary outcomes (including the primary outcome at 12-months, time to index ulcer healing,  
14  
15 326 reduction in ulcer area at 12-weeks, ulcer recurrence at 12-months, and quality of life) will be assessed  
16  
17 327 using various statistical models appropriate to the distribution and nature of these outcomes, with the  
18  
19 328 same modelling strategy as per the primary outcome above (e.g. missing data and appropriate model  
20  
21 329 diagnostics).

22  
23 330 The proportion healed at 12-months and the recurrence of the index ulcer at 12-months will be analysed  
24  
25 331 as the primary outcome above. The time to index ulcer healing will be analysed using a survival type  
26  
27 332 model (e.g. Cox proportional hazards model), and if the assumption regarding proportional hazards  
28  
29 333 fails, using a Restricted Mean Survival Time (RMST) approach. The reduction in area of the index ulcer  
30  
31 334 at 12 weeks over baseline will be analysed using a linear mixed model. The quality of life data (EQ-5D  
32  
33 335 and CCVUQ questionnaire) will be analysed using a repeated measures mixed linear models (with  
34  
35 336 repeated measures at 6-weeks, 6-months and 12-months and a suitable specified covariance  
36  
37 337 structure), with the overall treatment effect and the evolution of any treatment effect over time modelled.

### 38 39 338 **Cost-effectiveness analysis**

40  
41  
42 339 A literature review will be conducted to identify other economic studies and other trials in comparable  
43  
44 340 populations. A within-trial analysis and a decision model will be constructed. In both cases, the main  
45  
46 341 analyses will be performed from the perspective of the NHS and Personal Social Services. Secondary  
47  
48 342 analyses will be performed from a societal perspective. The price year will be 2018-2019. Discounting  
49  
50 343 will be applied according to UK Government guidelines. The study will be reported according to  
51  
52 344 consolidated guidelines for economic evaluation (CHEERS) (43).

53  
54 345 The within-trial analysis will compare the treatment strategies within the 12-month time horizon of the  
55  
56 346 clinical trial on an ITT basis. Data will be collected by case note review and questionnaires completed  
57  
58 347 at baseline and follow-up.

1  
2  
3 348 Resource use items in hospital and community care, adverse events or complications will be recorded  
4  
5 349 for each patient at 6- and 12-months. Resource use will be multiplied by UK unit costs obtained from  
6  
7 350 published literature, Healthcare Resource Groups, and manufacturers' list prices to calculate overall  
8  
9 351 costs. Utilities and QALYs will be calculated from the EQ-5D questionnaire. The extent of missing data  
10  
11 352 will be assessed and appropriate methods to handle missing data will be applied.

12  
13 353 The decision model provides a framework to incorporate evidence from other relevant studies and to  
14  
15 354 extrapolate outcomes, such as ulcer healing and recurrence, beyond the trial reporting period. The  
16  
17 355 Markov model will include the key ulcer-related health states and events that may occur during the  
18  
19 356 lifetime of the patient. The data to support extrapolation may be taken from the trial (e.g. fitting  
20  
21 357 parametric time-to-event functions to the trial data) or may come from external sources (such as the  
22  
23 358 literature review or observational data)(44,45).

24  
25 359 In both the within trial and model analyses, the incremental cost-effectiveness ratio will be calculated  
26  
27 360 and compared to current UK decision making thresholds. Sensitivity analysis will be carried out to test  
28  
29 361 the robustness of results to alternative assumptions about model structure or data. The cost-  
30  
31 362 effectiveness acceptability curve will be calculated using probabilistic sensitivity analysis (43).

### 32 33 363 **Data monitoring, safety and quality control**

34  
35 364 An independent Trial Steering Committee (TSC) and independent Data Monitoring Committee (iDMC)  
36  
37 365 have been appointed. The main role of the TSC is to provide overall supervision of the trial and ensure  
38  
39 366 that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the  
40  
41 367 relevant regulations, whilst the main role of the iDMC is to safeguard the interests of trial participants  
42  
43 368 and to monitor the main outcome measures including safety and efficacy. A clinical trial manager,  
44  
45 369 together with the Trial Management Group (TMG), will oversee trial progress.

46  
47 370 All treatment related adverse events (AEs; related to the skin graft or leg ulcer only) will be collected as  
48  
49 371 will all serious adverse events (SAEs). The chief investigator (CI) will be notified of all SAEs within 24  
50  
51 372 hours. All SAEs will be reported to the research ethics committee (REC) if, in the opinion of the CI, the  
52  
53 373 event was related to the intervention. All related AEs and SAEs will be recorded and summarised by  
54  
55 374 treatment strategy. These analyses will be descriptive, with any p-values calculated to be interpreted  
56  
57 375 descriptively.

## 376 **DISCUSSION**

377 Although compression therapy is the mainstay of treatment, there is a need to explore new treatments  
378 for wounds that are chronic and persistent in nature. This is the first randomised controlled trial to  
379 evaluate the use of DCD allograft for the treatment of VLU. This study will provide important data on  
380 whether the use of the DCD allograft plus standard care is associated with improved outcomes  
381 compared to standard care alone and will provide important data on its effects on quality of life and  
382 healthcare costs.

### 383 **Patient and public involvement**

384 Focus groups were held with patients accessing the vascular clinic at Imperial College Healthcare NHS  
385 Trust to obtain views on the proposed study and the acceptability of the DCD allograft. The focus group  
386 helped to inform important aspects of the trial, including the number of visits and questionnaires used  
387 in the study. A Patient and Public Involvement (PPI) representative was included as a co-applicant and  
388 provided invaluable input in the study design. A PPI representative also sits on the TSC, providing real  
389 time input on study progress. He will also aid with dissemination of the results.

390 **Ethics and dissemination:** Ethical approval was granted by the Bloomsbury Research Ethics  
391 Committee (19/LO/1271). Amendments to the protocol will be updated on the ISRCTN record. All  
392 amendments to the protocol will be submitted to the sponsor for review before applying for approval  
393 from the REC and the Health Research Authority (HRA). Standard informed consent will be taken with  
394 freedom to withdraw at any time. The findings from this study will be published in a peer-reviewed  
395 journal, presented at national and international conferences and to participants (via emails and letters  
396 at the end of the study).

397 **Current study status:** The current version of the protocol is v9.0. The study commenced recruitment  
398 in October 2019.

### 399 **Trial sponsor**

400 Imperial College London is the main sponsor for this study. Delegated responsibilities are assigned to  
401 the NHS trusts taking part in this study.

402

1  
2  
3 403 **Funding statement:** This study is supported by the J P Moulton Charitable Foundation. The DCD  
4  
5 404 allograft is provided free of charge by NHSBT. The design, management, analysis and reporting of the  
6  
7 405 study are entirely independent of J P Moulton Charitable Foundation and NHSBT.  
8

9  
10 406 **Availability of data and materials**

11 407 Data will be made available on reasonable request.  
12  
13 408

14  
15 409 **Author contributions**

16  
17 410 AHD, SO, TL, FH and LB were involved in the design of the study and securing funding. MG, KP, NC,  
18  
19 411 AB and KD were involved in the design of the study. AHD, SO and FH drafted the protocol and applied  
20  
21 412 for ethical approval. AHD and SO supervise the project. FH and SP coordinate the project. SO, AHD  
22  
23 413 and SP drafted the manuscript. JN and RLe will conduct the statistical analysis. DE will conduct the  
24  
25 414 cost-effectiveness analysis. AC and RLo advise on any DCD-related issues. All authors have read and  
26  
27 415 approved the final manuscript. AHD acts as guarantor.  
28

29  
30 416 **Competing interests**

31  
32 417 AC and RL are affiliated to NHS Blood and Transplant (NHSBT), who are providing the DCD  
33  
34 418 allografts free of charge. There are no other conflicts of interest to declare.  
35

36  
37 419 **Abbreviations**

38  
39  
40 420 ABPI: Ankle Brachial Pressure Index; AE: Adverse Event; CI: Chief Investigator; CCVUQ: Charing  
41  
42 421 Cross Venous Ulcer Questionnaire; CRN: Clinical Research Network; CHEERS: Consolidated Health  
43  
44 422 Economic Evaluation Reporting Standards; DCD: Decellularised dermis; EQ-5D: EuroQol Five-  
45  
46 423 Dimension; GP: General Practitioner; GCP: Good Clinical Practice; HRA: Health Research Authority;  
47  
48 424 ICER: Incremental Cost-Effectiveness Ratio; iDMC: Independent Data Monitoring Committee; ITT:  
49  
50 425 Intention-to-treat; ISRCTN: International Standard Randomised Controlled Trial Number; NHSBT:  
51  
52 426 National Health Service Blood and Transplant; NIHR: National Institute for Health Research; Patient  
53  
54 427 and Public Involvement: PPI; REDCap: Research Electronic Data Capture; REC: Research Ethics  
55  
56 428 Committee; RMST: Restricted Mean Survival Time; TMG: Trial Management Group; TSC: Trial Steering  
57  
58 429 Committee; QALY: Quality-adjusted life year; QoL: Quality of Life; Venous leg ulceration: VLU.  
59  
60

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437

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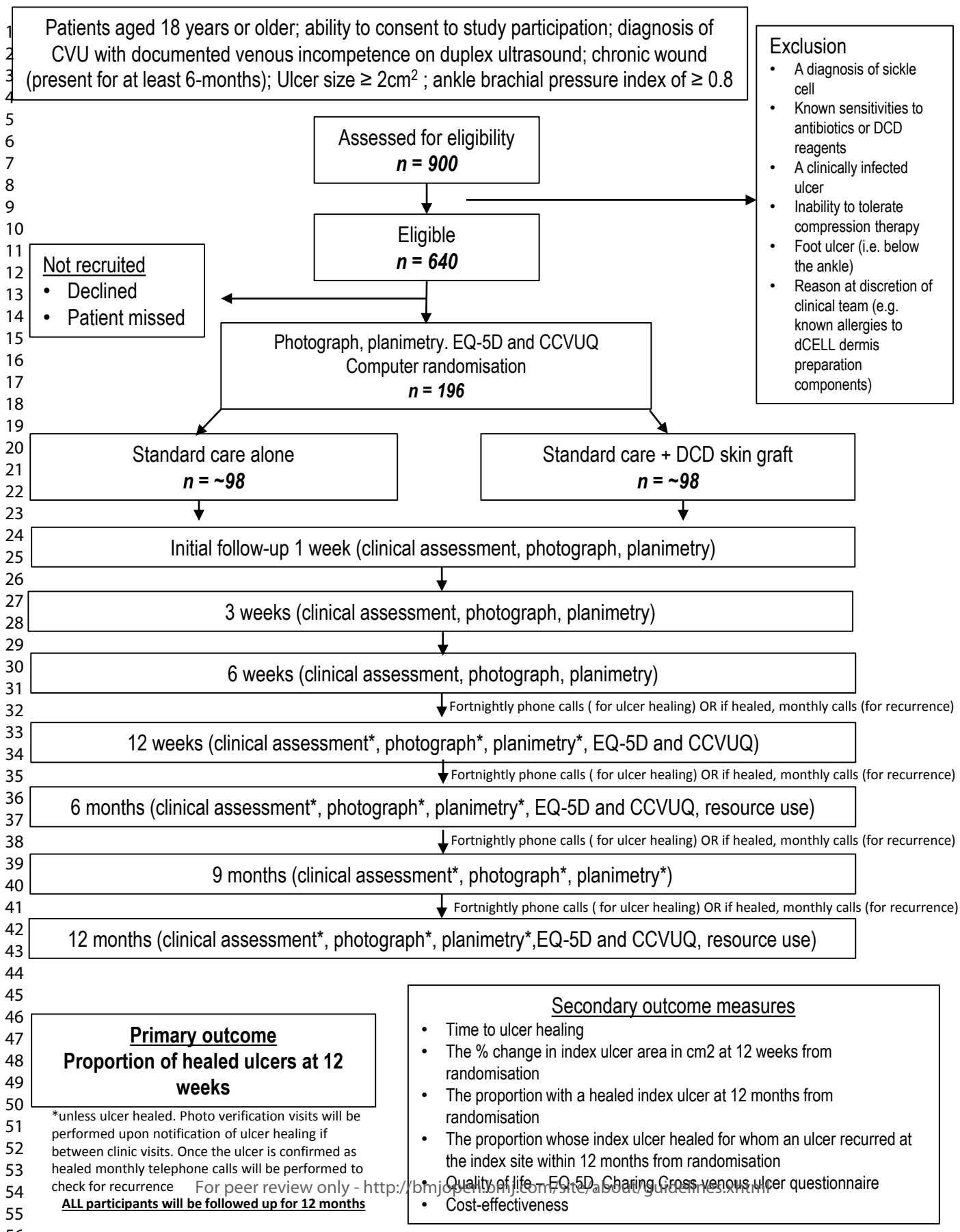
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29 567 Figure legend

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31 568 Figure 1: Flow diagram of the study protocol  
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**Figure 1: Flow diagram of the study protocol**





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____ 1 _____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____ 3 _____
	2b	All items from the World Health Organization Trial Registration Data Set	Included in trial registry and throughout manuscript
Protocol version	3	Date and version identifier	_____ 15 _____
Funding	4	Sources and types of financial, material, and other support	_____ 16 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1-2 _____
	5b	Name and contact information for the trial sponsor	_____ 15 _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____ 15 _____

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1	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____ 14 _____	
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10	<b>Introduction</b>			
11	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____ 5-7 _____
12	rationale			
13		6b	Explanation for choice of comparators	_____ 5-7 _____
14				
15				
16	Objectives	7	Specific objectives or hypotheses	_____ 7 _____
17				
18	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____ 7 _____
19				
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21				
22	<b>Methods: Participants, interventions, and outcomes</b>			
23				
24	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____ 8 _____
25				
26				
27	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____ 8 _____
28				
29				
30	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____ 8-9 _____
31				
32		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____ 10, 12 _____
33				
34		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____ N/A _____
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37		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____ 9 _____
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1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
6	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-12
10	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

19	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
25	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
33	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
36		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

**Methods: Data collection, management, and analysis**

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1	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	_8,12_
2	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of	
3			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	
4			Reference to where data collection forms can be found, if not in the protocol	
5				
6		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	___11-12___
7			collected for participants who discontinue or deviate from intervention protocols	
8				
9	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	___12___
10			(eg, double data entry; range checks for data values). Reference to where details of data management	
11			procedures can be found, if not in the protocol	
12				
13				
14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	___12-13___
15			statistical analysis plan can be found, if not in the protocol	
16				
17		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___10, 13-14_
18				
19		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	
20			statistical methods to handle missing data (eg, multiple imputation)	___12___
21				
22				
23	<b>Methods: Monitoring</b>			
24				
25	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	___14___
26			whether it is independent from the sponsor and competing interests; and reference to where further details	
27			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
28			needed	
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31		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	___10_
32			results and make the final decision to terminate the trial	
33				
34	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	___14___
35			events and other unintended effects of trial interventions or trial conduct	
36				
37	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	___N/A___
38			from investigators and the sponsor	
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41	<b>Ethics and dissemination</b>			
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1	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 15 ___
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4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 15 ___
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8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___ 10-11 ___
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12		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___ N/A ___
13				
14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___ 12 ___
15				
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18	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___ 16 ___
19				
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21	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ N/A ___
22				
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24	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___ N/A ___
25				
26				
27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___ 15 ___
28				
29		31b	Authorship eligibility guidelines and any intended use of professional writers	___ N/A ___
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___ 16 ___
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36	<b>Appendices</b>			
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38	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___ Provided on request ___
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1	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	___N/A___
2	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	

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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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# BMJ Open

## A study protocol for a multi-centre, randomised controlled trial to compare the use of the Decellularised Dermis Allograft in addition to standard care versus standard care alone for the treatment of Venous Leg Ulceration – DAVE trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041748.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2021
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<b>Primary Subject Heading</b>:	Cardiovascular medicine

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Secondary Subject Heading:	Nursing
Keywords:	VASCULAR MEDICINE, WOUND MANAGEMENT, Vascular surgery < SURGERY





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3 1 **Title:** A study protocol for a multi-centre, randomised controlled trial to compare the use of the  
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5 2 Decellularised Dermis Allograft in addition to standard care versus standard care alone for the treatment  
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7 3 of Venous Leg Ulceration – DAVE trial.

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10 52 **ABSTRACT**

11  
12 53 **Introduction:** Venous leg ulceration (VLU), the most common type of chronic ulcer, can be difficult to  
13  
14 54 heal and is a major cause of morbidity and reduced quality of life. Although compression bandaging is  
15  
16 55 the principal treatment, it is time consuming and bandage application requires specific training. There  
17  
18 56 is evidence that intervention on superficial venous incompetence can help ulcer healing and recurrence,  
19  
20 57 but this is not accessible to all patients. Hence, new treatments are required to address these chronic  
21  
22 58 wounds. One possible adjuvant treatment for VLU is human decellularised dermis (DCD), a type of skin  
23  
24 59 graft derived from skin from deceased tissue donors. Although DCD has the potential to promote ulcer  
25  
26 60 healing, there is a paucity of data for its use in patients with VLU.  
27

28 61 **Methods and analysis:** This is a multi-centre, parallel group, pragmatic randomised controlled trial.  
29  
30 62 One hundred and ninety-six patients with VLU will be randomly assigned to receive either the DCD  
31  
32 63 allograft in addition to standard care, or standard care alone. The primary outcome is the proportion of  
33  
34 64 participants with a healed index ulcer at 12-weeks post randomisation in each treatment arm.  
35  
36 65 Secondary outcomes include the time to index ulcer healing and the proportion of participants with a  
37  
38 66 healed index ulcer at 12-months. Changes in quality of life scores and cost-effectiveness will also be  
39  
40 67 assessed. All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic  
41  
42 68 regression on the outcome of the proportion of those with the index ulcer healed at 12-weeks, will be  
43  
44 69 performed. Secondary outcomes will be assessed using various statistical models appropriate to the  
45  
46 70 distribution and nature of these outcomes.  
47

48 71 **Ethics and dissemination:** Ethical approval was granted by the Bloomsbury Research Ethics  
49  
50 72 Committee (19/LO/1271). Findings will be published in a peer-reviewed journal and presented at  
51  
52 73 national and international conferences.  
53

54  
55 74 **Trial registration:** ISRCTN21541209.  
56

57 75 **Keywords:** Venous leg ulceration, decellularised dermis allograft, compression bandaging  
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**ARTICLE SUMMARY****Strengths and Limitations of the study**

- This is the first randomised controlled trial evaluating the use of the decellularised dermis (DCD) allograft solely in patients with venous leg ulceration (VLU).
- The cost-effectiveness analysis will assess the economic impact of utilising the DCD allograft for the management of patients with VLU.
- This is a pragmatic study hence compression and debridement technique will be up to local guidelines/standard care.
- This study only evaluates applications in patients with chronic venous ulceration.
- This study does not address long-term recurrence rates beyond 1 year.

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## 107 INTRODUCTION

### 108 Background and rationale

109 Venous leg ulceration (VLU) describes a persistent wound in the lower limbs caused by a poorly  
110 functioning venous system. Characterised by chronicity and a protracted and intensive treatment, these  
111 wounds affect approximately 1-2% of the population, with prevalence increasing to up to 4% in those  
112 over 65 years of age (1,2).

113 Venous leg ulceration has a devastating impact on quality of life and social function especially in the  
114 elderly (3–5). The wounds can be very painful, resulting in reduced mobility, and require regular  
115 dressing changes, which can be extremely painful and time-consuming. Together, these factors result  
116 in negative quality of life effects as severe as those seen in other life-limiting chronic conditions, such  
117 as congestive cardiac failure and chronic obstructive pulmonary disease (6).

118 Venous leg ulceration presents a significant burden to the healthcare service (7). Up to 50% of district  
119 nurse time is spent caring for people with chronic wounds, of which 70% will be venous in origin (8,9).  
120 Furthermore, ulcers can recur many times with up to 48% recurring at 5 years, thus requiring further  
121 treatment (10,11). Combined with the social cost due to loss of work and productivity, venous leg  
122 ulceration is estimated to cost up to 2% of the annual healthcare budget, which equates to  
123 approximately £2.5 billion in the UK in 2017 (12). This is predicted to increase as a result of the ageing  
124 population (13).

125 The management of chronic VLU is therefore an important priority and public health concern.  
126 Compression, in the form of bandaging and stockings, is the underlying principle of treatment, with the  
127 aim of reducing venous hypertension (14). However, applying compression is time consuming; bandage  
128 application requires skill and stockings are not suitable for everyone (14,15). Furthermore, the reduction  
129 in community nursing numbers has resulted in increasing difficulty for patients to access this service  
130 (16,17).

131 Evidence from the ESCHAR and EVRA trials show that interventions to abolish superficial venous  
132 incompetence improve ulcer healing and recurrence (8,18). Although promising, such intervention is  
133 not accessible to all patients (19). Moreover, although EVRA reported that early intervention performed

1  
2  
3 134 in ulcers with a duration of less than 6-months was beneficial, many patients present within leg  
4  
5 135 ulceration of greater duration than this, recurrent ulceration despite eradication of venous  
6  
7 136 incompetence, or may have underlying deep venous incompetence. These chronic wounds are known  
8  
9 137 to be hard to heal and require considerable nursing resources (10,20). The current treatments offered  
10  
11 138 are therefore insufficient for the management of VLU.

12  
13  
14 139 Skin grafting represents an adjuvant treatment that can promote and expedite ulcer healing (21). Grafts  
15  
16 140 can be taken from the patient's own skin, from a donor or from tissue engineered skin (22). An autograft  
17  
18 141 (graft from own skin) can be performed in different ways, including pinch and punch grafting, mincing  
19  
20 142 and meshing (23). Despite promoting ulcer healing, drawbacks exist, including poor cosmetic outcomes  
21  
22 143 and the need for a formal surgical procedure in an operating theatre in some instances (24,25).  
23  
24 144 Furthermore, surgical waiting lists can be lengthy and, in the current NHS climate, bed availability is not  
25  
26 145 guaranteed (26). Thus, routine autografts are not accessible to all ulcer patients. Allografts (donor skin)  
27  
28 146 and xenografts (animal skin) have been successfully employed, but present similar drawbacks to  
29  
30 147 autografts and the potential for immunogenicity and disease transmission (27). Tissue engineered skin  
31  
32 148 is donor skin that has been processed to be made inert, and therefore is not immunogenic (28). A  
33  
34 149 Cochrane review found that tissue-engineered skin in conjunction with compression increased the  
35  
36 150 healing rate in venous ulceration; however, there was insufficient evidence to determine the  
37  
38 151 effectiveness of any other skin graft material (29).

39  
40 152 Human decellularised dermis (DCD) is generated from skin donations from deceased tissue donors  
41  
42 153 processed to remove epidermal and dermal cells while preserving dermal structures and is supplied  
43  
44 154 nationally by NHS Blood and Transplant [(NHSBT) (30,31)]. This provides an immunologically inert  
45  
46 155 scaffold to support cellular repopulation and tissue re-vascularisation. Although allografts can only serve  
47  
48 156 as temporary cover, the advantage of the DCD allograft is that it can be applied to the wound with local  
49  
50 157 anaesthesia (via tissue staples or sutures) or without (via tissue glue), and therefore does not require  
51  
52 158 admission for a procedure under general anaesthetic. The procedure can be performed in the outpatient  
53  
54 159 department, avoiding inpatient admission and theatre use, making the technique more accessible to a  
55  
56 160 larger group of patients.

57  
58 161 The majority of DCD studies, including randomised controlled trials, have been performed in diabetic  
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1  
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3 162 populations (32–35). DCD allografts have been reported as safe, to promote angiogenesis (36) and, in  
4  
5 163 randomised controlled trials, to significantly reduce ulcer healing time (by up to 50%), (37,38). Cohort  
6  
7 164 study data reveals a reduction in wound surface area, improved healing in venous ulceration, with  
8  
9 165 evidence of angiogenesis, host cell migration and proliferation (39). This study addresses the lack of  
10  
11 166 robust research evidence about the effects of DCD allografts on VLU healing.

12  
13  
14 167 This prospective, randomised, open (non-blinded), pragmatic trial will explore whether the DCD allograft  
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16 168 in addition to standard care, compared to standard care alone, will improve healing rates, reduce  
17  
18 169 recurrence, increase ulcer-free time and improve quality of life for those with VLU. In addition, a cost-  
19  
20 170 effectiveness analysis will be performed to assess the economic impact of utilizing the DCD allograft  
21  
22 171 for the management of this patient population, whose care consumes significant financial resource.

23  
24 172 Currently, the annual cost to conservatively manage VLU is approximately £1,200 per patient (14);  
25  
26 173 however, in chronic ulceration this is likely to be more. The NHS per patient costs for graft application  
27  
28 174 will be approximately £400. If a positive outcome results from this trial, the reduced ulcer healing time  
29  
30 175 will likely result in significantly reduced NHS costs with an improvement in quality adjusted life years  
31  
32 176 (QALYs).

### 33 34 35 177 **Objectives**

36  
37  
38 178 The primary objective is to determine whether the use of the DCD allograft in patients with VLU, in  
39  
40 179 addition to standard care, improves healing at 12-weeks compared to standard care alone. Secondary  
41  
42 180 objectives include comparisons of time to ulcer healing, change in ulcer area at 12-weeks, ulcer  
43  
44 181 recurrence at 12-months, quality of life (QoL) assessment at 12-weeks, 6-months and 12-months and  
45  
46 182 cost-effectiveness analysis.

## 47 48 49 184 **METHODS AND ANALYSIS**

### 50 51 52 185 **Trial design**

53  
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55 186 This is a prospective, randomised, open (non-blinded), pragmatic trial with a follow-up of 12 months.

### 56 57 58 187 **Study Setting**

1  
2  
3 188 Eligible participants will be recruited from at least 10 sites in the United Kingdom. A full list of the study  
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5 189 sites can be found on the International Standard Randomised Controlled Trial Number (ISRCTN)  
6  
7 190 [registry \(ISRCTN21541209\)](https://www.isrctn.com/registry/ISRCTN21541209) (40).  
8  
9

### 10 191 **Eligibility Criteria**

11  
12 192 Inclusion criteria are: adult patients (> 18 years), able to provide informed consent with a diagnosis of  
13 193 VLU with documented evidence of venous incompetence on duplex ultrasound, ulcer duration for > 6-  
14 194 months and ulcer surface area  $\geq 2$  cm<sup>2</sup>. Where there is more than one ulcer present, the largest ulcer  
15 195 will be chosen as the index ulcer for the purposes of the trial. Exclusion criteria include: a diagnosis of  
16 196 sickle cell disease, an ankle brachial pressure index (ABPI) < 0.8, a clinically infected ulcer, treatment  
17 197 with biomedical or topical growth factors within the previous 30 days, a previous history of an inability  
18 198 to tolerate compression therapy or a foot ulcer (i.e. below the ankle). The DCD allograft preparation  
19 199 entails the use of a number of components, including specific antibiotics, which are then washed  
20 200 away. There have been no documented allergic or hypersensitivity reactions to the DCD graft  
21 201 reported. Patients with known allergies to the DCD preparation components are therefore able to  
22 202 participate at the discretion of the clinical team.  
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### 34 203 **Interventions**

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36 204 All eligible patients will be informed about the study and provided with a written information sheet.  
37 205 Consenting participants will be randomised to receive either the DCD allograft in addition to standard  
38 206 care or standard care alone (Figure 1). Baseline demographic data will be collected for each participant,  
39 207 including details of their past medical history and any concomitant medication. The EQ-5D (41) and  
40 208 Charing Cross Venous Ulceration Questionnaire (CCVUQ) (42) will also be completed for generic and  
41 209 disease-specific quality of life assessment respectively.  
42  
43  
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49 210 Participants in the standard care arm will undergo wound cleaning and debridement, plus standard  
50 211 compression therapy in the form of multilayer elastic compression bandaging or stockings.

51 212 Participants in the DCD arm will undergo wound cleaning and debridement and DCD allograft  
52 213 application. The DCD graft will be applied by trained registered healthcare professionals (physicians  
53 214 or nurses). Training on the application of the DCD graft will be provided by NHSBT. The DCD will be  
54 215 applied to the debrided index ulcer wound bed. Recommendations will be made that the DCD should  
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3 216 be secured with surgical glue, staples and/or sutures to optimise graft adhesion. The DCD graft  
4  
5 217 should be fenestrated liberally with a scalpel or scissors to allow wound exudate to pass through to  
6  
7 218 reduce risk of seroma/haematoma developing under DCD. Following application of the DCD allograft,  
8  
9 219 a non-adhesive, non-absorbent, non-medicated primary dressing will be applied, followed by the  
10  
11 220 appropriate bolster/secondary dressings (31). Compression therapy will then be applied according to  
12  
13 221 local practice and may include multilayer elastic compression bandaging or stockings delivering 20 to  
14  
15 222 40mm/Hg pressure. Practice/district nurses will be advised not to change the primary dressing the first  
16  
17 223 7-days post DCD allograft application. If the DCD allograft has not adhered to the wound bed at the 1-  
18  
19 224 week visit, the graft can be rinsed in saline (if it appears viable) and reapplied and re-secured.  
20  
21 225 Additional grafts will not be reapplied as part of the trial.  
22

23 226

24  
25 227 [Figure 1 about here]  
26

27  
28 228 As this is a pragmatic trial, the ulcer care in both arms will be as per local unit standard practice. All  
29  
30 229 participants will have their ulcers irrigated, cleaned and debrided according to best local practice.  
31  
32 230 Compression therapy will be according to local practice and may include multilayer elastic compression  
33  
34 231 bandaging or stockings designed to deliver between 20 to 40mm/Hg pressure. Wound dressing and  
35  
36 232 compression application will be performed by trained research nurses or community/district/practice  
37  
38 233 nurses as per standard care. In the event of a missed visit, local study teams will liaise with/ask the  
39  
40 234 participant to liaise with the district/community/practice nurse to arrange dressing change and  
41  
42 235 compression application. The use of negative pressure wound therapy device will be left to the  
43  
44 236 discretion of the treating clinician. All participants may be offered interventional procedures in the form  
45  
46 237 of endovenous ablation (in the presence of superficial venous disease) dependent on whether local  
47  
48 238 recruitment site practice is to intervene upon ulcers over 6 months' duration. Once the wound has  
49  
50 239 healed, the participant will be given a minimum of Class II compression hosiery (18 – 24 mmHg) to wear  
51  
52 240 to prevent ulcer recurrence as per local practice. Endovenous ablation, amongst other procedures, at  
53  
54 241 any point post-randomisation, will be recorded at the 12-month follow-up.

55 242 **Primary outcome**  
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57  
58 243 The primary outcome is the proportion of participants with a healed index ulcer assessed with ulcer  
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3 244 photography at 12 weeks after randomisation. **Secondary outcomes**

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5  
6 245 The secondary outcomes include:

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9 246 • Time to index ulcer healing from randomisation
- 10  
11 247 • The percentage change in index ulcer area at 12-weeks from randomisation
- 12  
13 248 • The proportion of participants with a healed index ulcer at 12-months from randomisation
- 14  
15 249 • The proportion of those whose index ulcer healed for whom an ulcer recurred at the index site
- 16  
17 250 within 12-months from randomisation
- 18  
19 251 • Change in QoL score at 12-weeks, 6-months and 12-months from randomisation using the EQ-
- 20  
21 252 5D and CCVUQ
- 22  
23 253 • Cost-effectiveness analysis, measured using the Incremental Cost-Effectiveness Ratio (ICER)

24  
25  
26 254 **Sample Size and study duration**

27  
28 255 To detect an absolute difference of 25% in the proportion of participants with a healed index ulcer at 12

29  
30 256 weeks (assuming a healing rate of 30% in the control group and 55% in the intervention group) and

31  
32 257 allowing for a 10% loss to follow up with a power of 90% and 5% level of significance, 196 patients are

33  
34 258 required (Stata/IC 15.1 for Mac, Statacorp, College Station, Texas, USA; procedure 'power twoprop',

35  
36 259 with continuity correction). The effect size was estimated from previously published literature on diabetic

37  
38 260 and venous ulceration, showing an absolute difference in the proportion of participants with a healed

39  
40 261 ulcer of 25% between intervention and control groups at 12 weeks (32,38,39). With the 12-month follow-

41  
42 262 up, this study will run for 36-months.

43  
44  
45 263 **Interim analysis**

46  
47 264 When we have mature 12-week primary outcome data on the first 50 participants randomised, we will

48  
49 265 review the sample size with the independent TSC on the basis of recruitment rate, the overall (blinded)

50  
51 266 primary outcome of index ulcer healed proportion (expected to be  $(30+55/2) \approx 40\%$ ) and attrition rate

52  
53 267 (expected to be 10%).

54  
55 268

56  
57 269 We plan on having a formal interim analysis with the possibility of stopping early for futility (no prospect

58  
59 270 of a clinically meaningful treatment effect, or for overwhelming evidence of effectiveness) at this point

1  
2  
3 271 (of n=50 with mature primary outcome data, or at around 25% of the total scheduled events observed).  
4  
5 272 This single interim analysis using a Lan-DeMets alpha spending approach with Fleming O'Brien  
6  
7 273 boundaries has negligible effect on the required sample size (R 3.4.1 for Windows, package gsDesign).  
8  
9

#### 10 274 **Recruitment**

11  
12  
13 275 Potential participants will be identified at outpatient clinic appointments. Posters and leaflets will also  
14  
15 276 be displayed in the outpatient clinics and other appropriate locations.

16  
17  
18 277 Potentially eligible patients will receive a verbal explanation of the study and a patient information sheet  
19  
20 278 by the attending clinical/research team.

#### 21 22 279 **Randomisation**

23  
24  
25 280 Consent forms are completed on the day of treatment. Following confirmation of eligibility, consent and  
26  
27 281 completion of baseline assessments, participants will then be randomly allocated to receive one of the  
28  
29 282 two possible treatment options using an online computerised web system (REDCap, managed by the  
30  
31 283 study data centre, University of Edinburgh). A minimization algorithm using centre, index ulcer size and  
32  
33 284 duration will be used, including a random component to lessen predictability.

#### 34 35 36 285 **Blinding**

37  
38  
39 286 As the DCD allograft is visible after application for a period of time, it is not possible to mask participants  
40  
41 287 or the research/clinical teams to the treatment strategy. However the primary outcome assessments  
42  
43 288 (verification of index ulcer healing visits) will be completed by an independent clinical assessor trained  
44  
45 289 in the assessment of wound healing, who will have no previous involvement with, or knowledge of, the  
46  
47 290 participant's index ulcer treatment and as such will be blind to the randomised treatment strategy (the  
48  
49 291 DCD allograft is not expected to be visible after 4 weeks).

#### 50 51 292 **Follow-up periods**

52  
53  
54 293 All participants will attend for follow-up at 1-week, 3-weeks, 6-weeks and 12-weeks, 6-months, 9-  
55  
56 294 months and 12-months post-randomisation. At all follow-up visits, a clinical assessment will be  
57  
58 295 undertaken and a photograph and planimetry tracing of the ulcer will be collected (unless healing has  
59  
60



1  
2  
3 296 been confirmed). The EQ-5D and the CCVUQ will be collected at baseline and the 12-week, 6- and 12-  
4  
5 297 month follow-ups. Healthcare resource use (procedures, hospital, GP and community nurse visits,  
6  
7 298 physiotherapy and other interventions), days lost from work and normal activities, carer time and out-  
8  
9 299 of-pocket expenses related to leg ulcer care will also be collected from case notes and patient diaries  
10  
11 300 during the initial procedure and at 6- and 12-months.

12  
13  
14 301 Fortnightly calls will be made after the 6-week follow-up to check if the ulcer has healed. If the  
15  
16 302 participant reports that their ulcer has healed, they will be invited to attend a verification visit, where a  
17  
18 303 photograph of the ulcer will be taken. This photograph will be sent to an independent assessor  
19  
20 304 (blinded to treatment allocation) for assessment and confirmation of healing status. Ulcer healing is  
21  
22 305 defined as complete re-epithelialisation of the index ulcer in the absence of a scab (eschar) with no  
23  
24 306 dressing required confirmed by blinded photo assessment of healing.

25  
26 307 If the ulcer is confirmed as healed, monthly telephone calls will be performed to check for recurrence.  
27  
28 308 In the event that an ulcer is confirmed as healed, the recurrence, safety, resource use and health  
29  
30 309 questionnaire data can be collected over the telephone or by post. If the participant fails to attend their  
31  
32 310 appointment, attempts will be made to collect the QoL and patient resource use diaries by telephone or  
33  
34 311 post. Participants will receive up to £10 for each visit attended as a contribution towards travel  
35  
36 312 expenses.

### 37 38 39 313 **Data collection and confidentiality**

40  
41 314 Participant data will be stored in the password-protected REDCap database. Participant details will be  
42  
43 315 anonymised as each participant will be allocated a participant number. Identifiable data, including  
44  
45 316 contact information, will also be recorded on paper forms and will be kept in a locked filing cabinet in a  
46  
47 317 locked office at each investigational site. Data will be monitored for quality and completeness and  
48  
49 318 missing data will be requested from the participating sites, as per the data monitoring plan.

### 50 51 52 319 **Statistical analysis**

53  
54  
55 320 All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic regression  
56  
57 321 on the outcome of the proportion of those with the index ulcer healed at 12-weeks, with site as a random  
58  
59 322 effect and randomised group as the treatment effect, along with index ulcer size and duration at baseline



1  
2  
3 323 (the minimisation factors) and any other baseline factors known or suspected to be strongly related to  
4  
5 324 good or poor outcome, will form the model. Goodness of model fit will be examined using the Hosmer-  
6  
7 325 Lemeshow approach. The robustness of the findings to any patterns of missing data (both assuming  
8  
9 326 data are missing at random; and, if appropriate, informatively missing (missing not at random)) will be  
10  
11 327 explored using appropriate sensitivity analyses.

12  
13 328 Secondary outcomes (including the primary outcome at 12-months, time to index ulcer healing,  
14  
15 329 reduction in ulcer area at 12-weeks, ulcer recurrence at 12-months, and quality of life) will be assessed  
16  
17 330 using various statistical models appropriate to the distribution and nature of these outcomes, with the  
18  
19 331 same modelling strategy as per the primary outcome above (e.g. missing data and appropriate model  
20  
21 332 diagnostics).

22  
23 333 The proportion healed at 12-months and the recurrence of the index ulcer at 12-months will be analysed  
24  
25 334 as the primary outcome above. The time to index ulcer healing will be analysed using a survival type  
26  
27 335 model (e.g. Cox proportional hazards model), and if the assumption regarding proportional hazards  
28  
29 336 fails, using a Restricted Mean Survival Time (RMST) approach. The reduction in area of the index ulcer  
30  
31 337 at 12 weeks over baseline will be analysed using a linear mixed model. The quality of life data (EQ-5D  
32  
33 338 and CCVUQ questionnaire) will be analysed using a repeated measures mixed linear models (with  
34  
35 339 repeated measures at 12-weeks, 6-months and 12-months and a suitable specified covariance  
36  
37 340 structure), with the overall treatment effect and the evolution of any treatment effect over time modelled.

### 38 39 341 **Cost-effectiveness analysis**

40  
41  
42 342 A literature review will be conducted to identify other economic studies and other trials in comparable  
43  
44 343 populations. A within-trial analysis and a decision model will be constructed. In both cases, the main  
45  
46 344 analyses will be performed from the perspective of the NHS and Personal Social Services. Secondary  
47  
48 345 analyses will be performed from a societal perspective. The price year will be 2018-2019. Discounting  
49  
50 346 will be applied according to UK Government guidelines. The study will be reported according to  
51  
52 347 consolidated guidelines for economic evaluation (CHEERS) (43).

53  
54 348 The within-trial analysis will compare the treatment strategies within the 12-month time horizon of the  
55  
56 349 clinical trial on an ITT basis. Data will be collected by case note review and questionnaires completed  
57  
58 350 at baseline and follow-up.

1  
2  
3 351 Resource use items in hospital and community care, adverse events or complications will be recorded  
4  
5 352 for each patient at 6- and 12-months. Resource use will be multiplied by UK unit costs obtained from  
6  
7 353 published literature, Healthcare Resource Groups, and manufacturers' list prices to calculate overall  
8  
9 354 costs. Utilities and QALYs will be calculated from the EQ-5D questionnaire. The extent of missing data  
10  
11 355 will be assessed and appropriate methods to handle missing data will be applied.

12  
13 356 The decision model provides a framework to incorporate evidence from other relevant studies and to  
14  
15 357 extrapolate outcomes, such as ulcer healing and recurrence, beyond the trial reporting period. The  
16  
17 358 Markov model will include the key ulcer-related health states and events that may occur during the  
18  
19 359 lifetime of the patient. The data to support extrapolation may be taken from the trial (e.g. fitting  
20  
21 360 parametric time-to-event functions to the trial data) or may come from external sources (such as the  
22  
23 361 literature review or observational data)(44,45).

24  
25 362 In both the within trial and model analyses, the incremental cost-effectiveness ratio will be calculated  
26  
27 363 and compared to current UK decision making thresholds. Sensitivity analysis will be carried out to test  
28  
29 364 the robustness of results to alternative assumptions about model structure or data. The cost-  
30  
31 365 effectiveness acceptability curve will be calculated using probabilistic sensitivity analysis (43).

### 32 33 366 **Data monitoring, safety and quality control**

34  
35 367 An independent Trial Steering Committee (TSC) and independent Data Monitoring Committee (iDMC)  
36  
37 368 have been appointed. The main role of the TSC is to provide overall supervision of the trial and ensure  
38  
39 369 that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the  
40  
41 370 relevant regulations, whilst the main role of the iDMC is to safeguard the interests of trial participants  
42  
43 371 and to monitor the main outcome measures including safety and efficacy. A clinical trial manager,  
44  
45 372 together with the Trial Management Group (TMG), will oversee trial progress.

46  
47 373 All treatment related adverse events (AEs; related to the skin graft or leg ulcer only) will be collected as  
48  
49 374 will all serious adverse events (SAEs). The chief investigator (CI) will be notified of all SAEs within 24  
50  
51 375 hours. All SAEs will be reported to the research ethics committee (REC) if, in the opinion of the CI, the  
52  
53 376 event was related to the intervention. All related AEs and SAEs will be recorded and summarised by  
54  
55 377 treatment strategy. These analyses will be descriptive, with any p-values calculated to be interpreted  
56  
57 378 descriptively.

## 379 **DISCUSSION**

380 Although compression therapy is the mainstay of treatment, there is a need to explore new treatments  
381 for wounds that are chronic and persistent in nature. This is the first randomised controlled trial to  
382 evaluate the use of DCD allograft for the treatment of VLU. This study will provide important data on  
383 whether the use of the DCD allograft plus standard care is associated with improved outcomes  
384 compared to standard care alone and will provide important data on its effects on quality of life and  
385 healthcare costs.

### 386 **Patient and public involvement**

387 Focus groups were held with patients accessing the vascular clinic at Imperial College Healthcare NHS  
388 Trust to obtain views on the proposed study and the acceptability of the DCD allograft. The focus group  
389 helped to inform important aspects of the trial, including the number of visits and questionnaires used  
390 in the study. A Patient and Public Involvement (PPI) representative was included as a co-applicant and  
391 provided invaluable input in the study design. A PPI representative also sits on the TSC, providing real  
392 time input on study progress. He will also aid with dissemination of the results.

393 **Ethics and dissemination:** Ethical approval was granted by the Bloomsbury Research Ethics  
394 Committee (19/LO/1271). Amendments to the protocol will be updated on the ISRCTN record. All  
395 amendments to the protocol will be submitted to the sponsor for review before applying for approval  
396 from the REC and the Health Research Authority (HRA). Standard informed consent will be taken with  
397 freedom to withdraw at any time. The findings from this study will be published in a peer-reviewed  
398 journal, presented at national and international conferences and to participants (via emails and letters  
399 at the end of the study).

400 **Current study status:** The current version of the protocol is v9.0. The study commenced recruitment  
401 in October 2019.

### 402 **Trial sponsor**

403 Imperial College London is the main sponsor for this study. Delegated responsibilities are assigned to  
404 the NHS trusts taking part in this study.

405

1  
2  
3 406 **Funding statement:** This study is supported by the J P Moulton Charitable Foundation (grant number:  
4  
5 407 N/A). The DCD allograft is provided free of charge by NHSBT. The design, management, analysis and  
6  
7 408 reporting of the study are entirely independent of J P Moulton Charitable Foundation and NHSBT.  
8

9  
10 409 **Availability of data and materials**

11 410 Data will be made available on reasonable request.  
12  
13 411

14  
15 412 **Author contributions**

16  
17 413 AHD, SO, TL, FH and LB were involved in the design of the study and securing funding. MG, KP, NC,  
18  
19 414 AB and KD were involved in the design of the study. AHD, SO and FH drafted the protocol and applied  
20  
21 415 for ethical approval. AHD and SO supervise the project. FH and SP coordinate the project. SO, AHD  
22  
23 416 and SP drafted the manuscript. JN and RLe will conduct the statistical analysis. DE will conduct the  
24  
25 417 cost-effectiveness analysis. AC and RLo advise on any DCD-related issues. All authors have read and  
26  
27 418 approved the final manuscript. AHD acts as guarantor.  
28

29  
30 419 **Competing interests**

31  
32 420 AC and RL are affiliated to NHS Blood and Transplant (NHSBT), who are providing the DCD  
33  
34 421 allografts free of charge. There are no other conflicts of interest to declare.  
35  
36

37 422 **Abbreviations**

38  
39  
40 423 ABPI: Ankle Brachial Pressure Index; AE: Adverse Event; CI: Chief Investigator; CCVUQ: Charing  
41  
42 424 Cross Venous Ulcer Questionnaire; CRN: Clinical Research Network; CHEERS: Consolidated Health  
43  
44 425 Economic Evaluation Reporting Standards; DCD: Decellularised dermis; EQ-5D: EuroQol Five-  
45  
46 426 Dimension; GP: General Practitioner; GCP: Good Clinical Practice; HRA: Health Research Authority;  
47  
48 427 ICER: Incremental Cost-Effectiveness Ratio; iDMC: Independent Data Monitoring Committee; ITT:  
49  
50 428 Intention-to-treat; ISRCTN: International Standard Randomised Controlled Trial Number; NHSBT:  
51  
52 429 National Health Service Blood and Transplant; NIHR: National Institute for Health Research; Patient  
53  
54 430 and Public Involvement: PPI; REDCap: Research Electronic Data Capture; REC: Research Ethics  
55  
56 431 Committee; RMST: Restricted Mean Survival Time; TMG: Trial Management Group; TSC: Trial Steering  
57  
58 432 Committee; QALY: Quality-adjusted life year; QoL: Quality of Life; Venous leg ulceration: VLU.  
59  
60

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440

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29 570 Figure legend

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31 571 Figure 1: Flow diagram of the study protocol

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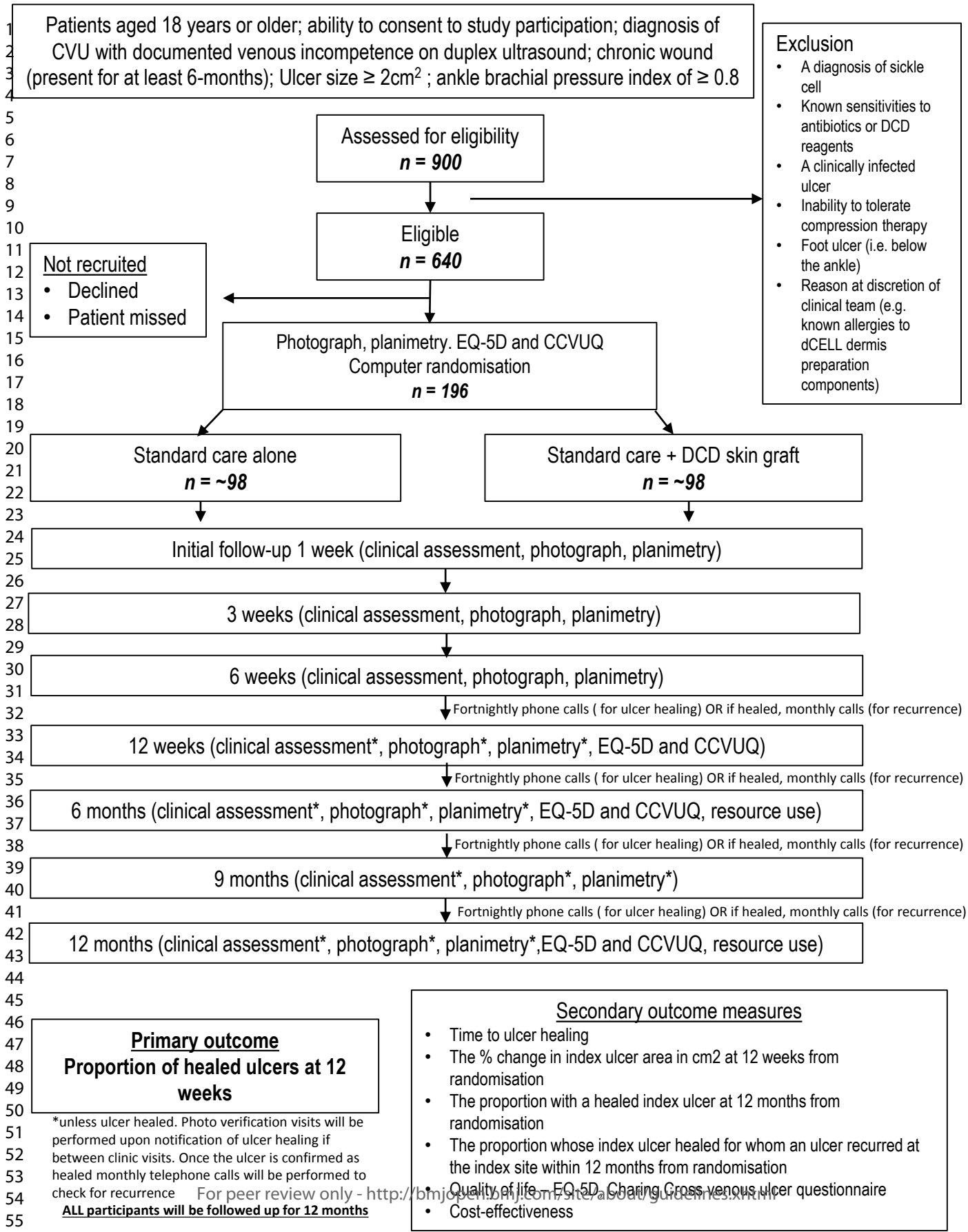
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For peer review only

**Figure 1: Flow diagram of the study protocol**





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____ 1 _____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____ 3 _____
	2b	All items from the World Health Organization Trial Registration Data Set	Included in trial registry and throughout manuscript
Protocol version	3	Date and version identifier	_____ 15 _____
Funding	4	Sources and types of financial, material, and other support	_____ 16 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1-2 _____
	5b	Name and contact information for the trial sponsor	_____ 15 _____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____ 15 _____

1 5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint  
 2 adjudication committee, data management team, and other individuals or groups overseeing the trial, if  
 3 applicable (see Item 21a for data monitoring committee) \_\_\_\_\_ 14 \_\_\_\_\_  
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8  
 9 **Introduction**

10  
 11 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant  
 12 rationale studies (published and unpublished) examining benefits and harms for each intervention \_\_\_\_\_ 5-7 \_\_\_\_\_  
 13

14 6b Explanation for choice of comparators \_\_\_\_\_ 5-7 \_\_\_\_\_  
 15

16 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 7 \_\_\_\_\_  
 17

18 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),  
 19 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_\_\_ 7 \_\_\_\_\_  
 20  
 21

22 **Methods: Participants, interventions, and outcomes**

23  
 24 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will  
 25 be collected. Reference to where list of study sites can be obtained \_\_\_\_\_ 8 \_\_\_\_\_  
 26

27 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  
 28 individuals who will perform the interventions (eg, surgeons, psychotherapists) \_\_\_\_\_ 8 \_\_\_\_\_  
 29

30 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be  
 31 administered \_\_\_\_\_ 8-9 \_\_\_\_\_  
 32

33 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  
 34 change in response to harms, participant request, or improving/worsening disease) \_\_\_\_\_ 10, 12 \_\_\_\_\_  
 35

36 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence  
 37 (eg, drug tablet return, laboratory tests) \_\_\_\_\_ N/A \_\_\_\_\_  
 38

39 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 9 \_\_\_\_\_  
 40  
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 42

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1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
6	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-12
10	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

19	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
25	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
33	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
36		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

### Methods: Data collection, management, and analysis

1	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	_8,12_
2	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of	
3			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	
4			Reference to where data collection forms can be found, if not in the protocol	
5				
6		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	___11-12___
7			collected for participants who discontinue or deviate from intervention protocols	
8				
9	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	___12___
10			(eg, double data entry; range checks for data values). Reference to where details of data management	
11			procedures can be found, if not in the protocol	
12				
13				
14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	___12-13___
15			statistical analysis plan can be found, if not in the protocol	
16				
17		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___10, 13-14_
18				
19		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	
20			statistical methods to handle missing data (eg, multiple imputation)	___12___
21				
22				
23	<b>Methods: Monitoring</b>			
24				
25	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	___14___
26			whether it is independent from the sponsor and competing interests; and reference to where further details	
27			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
28			needed	
29				
30				
31		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	___10_
32			results and make the final decision to terminate the trial	
33				
34	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	___14___
35			events and other unintended effects of trial interventions or trial conduct	
36				
37	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	___N/A___
38			from investigators and the sponsor	
39				
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41	<b>Ethics and dissemination</b>			
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1	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 15 ___
2				
3				
4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ 15 ___
5				
6				
7				
8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___ 10-11 ___
9				
10				
11				
12		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___ N/A ___
13				
14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___ 12 ___
15				
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18	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___ 16 ___
19				
20				
21	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ N/A ___
22				
23				
24	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___ N/A ___
25				
26				
27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___ 15 ___
28				
29		31b	Authorship eligibility guidelines and any intended use of professional writers	___ N/A ___
30				
31		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___ 16 ___
32				
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36	<b>Appendices</b>			
37				
38	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___ Provided on request ___
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1 Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular  
2 analysis in the current trial and for future use in ancillary studies, if applicable  
3

\_\_\_N/A\_\_\_

4 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
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