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HAWS

Haemoglobin Application to Wounds Study

HAWS; Haemoglobin Application to Wounds Study, a single-centre, controlled, prospective randomized trial

Version 6, dd 10July 2018

Chief Investigator's Statement of Ownership and Content.

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

Name (PRINT): DR STACEY FISHER

Signature: _____

Date: 14TH SEP. 2018

RESEARCH PROTOCOL SUMMARY

TITLE:	Haemoglobin Application to Wounds Study, a single-centre, controlled, prospective, randomized trial of Granulox haemoglobin spray for adjuvant treatment of foot ulcers
Short title:	HAWS; Haemoglobin Application to Wounds Study
IRAS number	227421
Device description	Granulox® Medical device. Class III, CE 0482 Indications: Granulox® is a spray for use on chronic wounds. Granulox® is an innovative medical device for the proposed treatment of chronic wounds, such as venous leg ulcer, arterial leg ulcer, mixed leg ulcer, foot ulcers, secondary healing of surgical wounds and pressure sores. Granulox® can also be used on sloughy and infected wounds. Each canister contains 12 ml of spray, sufficient for 30 wound treatments.
Study design	Single-centre, controlled, prospective randomized trial
Primary objective	To determine the efficacy of the Granulox spray as an adjuvant therapy for foot ulcers at 3, 6, 9 and 12 weeks post-baseline - Healing rate (ulcer size; 12 weeks is endpoint for power calculation), as measured with surface area scoring grid
Secondary objectives	Clinical assessment at -2, 0, 3, 6, 9 and 12 weeks, and - PUSH ulcer size/grading score - Texas Univ grading score - Wound closure Safety of Granulox spray throughout trial duration, up to 12 weeks - Wound infection incidence; secondary interventions Patient-reported outcome measures at 0, 6 and 12 weeks - Patient mobility score (LifeSpace questionnaire) - Quality of life score (EQ-5D-5L and CWIQ) - Visual Analogue Score for pain associated with DFU Status of wound at week 18 - Healed, not healed, recurrence.
Patient population	A total of 60 participants, over the age of eighteen, with measurable foot ulcer, treated in clinic. Forty patients to have a DFU and further 20 patients to have nondiabetes related foot

	ulcer. Participants must have the capacity to provide informed written consent and complete patient reported outcome measures. - 30 Patient will receive treatment as usual (TaU) - 30 Patients will receive TaU plus adjuvant Granulox application twice weekly. Randomisation will be stratified for diabetes diagnosis (yes/no) and ulcer size, with cut-off PUSH score of 6 and above, or 5 or less. Patients will first go through a two week screening period; those patients with a healing rate of > 50% in 2 weeks will not be eligible for the intervention period.
Sponsor	Cumbria Partnership NHS Foundation Trust
Manufacturer & research grant provider	SASTOMED GMBH, https://granulox.de/en/sastomed contact: Dr. Peter Engels, EngelsConsult Gartenstr. 25, 51429 Bergisch Gladbach Phone: +49 2204 963653; Mobile : +49 172 522 2104 engels@engelsconsult.de
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Organisation where research will take place	Cumbria Partnership NHS Foundation Trust Carleton Clinic R&D department Cumwhinton Drive Carlisle CA1 3SX Phone: 01228 602000

Planned timeline	Recruitment start date (first patient, first visit) July 2017, Recruitment end date (last patient, first visit): 31 Jan 2019 Trial end date: Apr 2019
Protocol version, date	Version 6, 10 July 2018

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1. LAY SUMMARY

Peripheral vascular disease (PVD) and diabetes can lead to various complications in affected people, and they include (diabetic) foot ulcers. Foot ulcers carry with it high levels of morbidity and can lead to further complications such as infection in the ulcer and amputation of the foot. If a foot ulcer develops, it is important to treat it appropriately in order to optimise the chance of the foot ulcer healing and minimise the risk of infection, respectively. The application of dressings and so-called offloading of the foot ulcer area reduces the strain on the wound area and keeps it clean. To allow optimal healing of the wound, it is essential to have sufficiently high oxygen levels. Lack of it, hypoxia, can lead to necrosis and deterioration of the wound. Oxygen promotes the formation of new blood vessels and subsequently the growth of new skin.

New treatment modalities have been introduced to increase oxygen levels in wounds, including hyperbaric oxygen (HBO) treatment. However, such treatments tend to be cumbersome, time-intensive and costly. In the UK, InFirst Ltd has brought to market a new medical device for oxygen treatment, which is designed to be more straightforward to apply than HBO. The product, Granulox, contains porcine haemoglobin contained in a spray canister. It is applied twice weekly to a wound during redressing, ie including foot ulcers, and can be used in a clinic or patient's home setting. Initial case series and retrospective comparative studies have shown that Granulox reduces the time for a foot ulcer to heal.

This study seeks to assess if Granulox has a significant positive impact on the rate of wound healing in foot ulcers. For the first time, a prospective randomised approach is taken, which is a scientifically more solid approach than the case series published to date. This means that by virtue of a computer deciding the type of treatment, participants will receive standard care or standard care plus Granulox spray twice weekly for up to 12 weeks or until the foot ulcer is healed. The effects of the trial treatment on participants' quality of life and its safety will also be appraised.

2. INTRODUCTION

The occurrence of foot ulcers has enormous cost complications. Figures available for diabetic foot ulcer (DFU) alone total £650 million per year once associated morbidity is taken into account (NHS Diabetes report). Non-healing ulcers may lead to bacterial infection of wounds and increase the risk of further degenerative complications including cellulitis, necrotising fasciitis, and sepsis (Grothier, 2015). Specific wounds, again including diabetic foot ulcers, may lead to amputation if osteomyelitis develops. An additional undesirable effect of infected wounds is that it delays – or stops altogether – the wound healing process (Halbert et al, 1992). Therefore, enhancement of foot ulcer healing rate is desirable to minimise morbidity and healthcare costs. Table 1 shows annual NHS cost for treating DFUs compared to other chronic wound treatments. Other foot ulcers are commonly caused by venous insufficiency, and therefore the cost of managing them falls within the venous leg ulcer category of Table 1.

Table 1. Chronic wound treatment costs to the NHS (Posnett & Franks 2008)

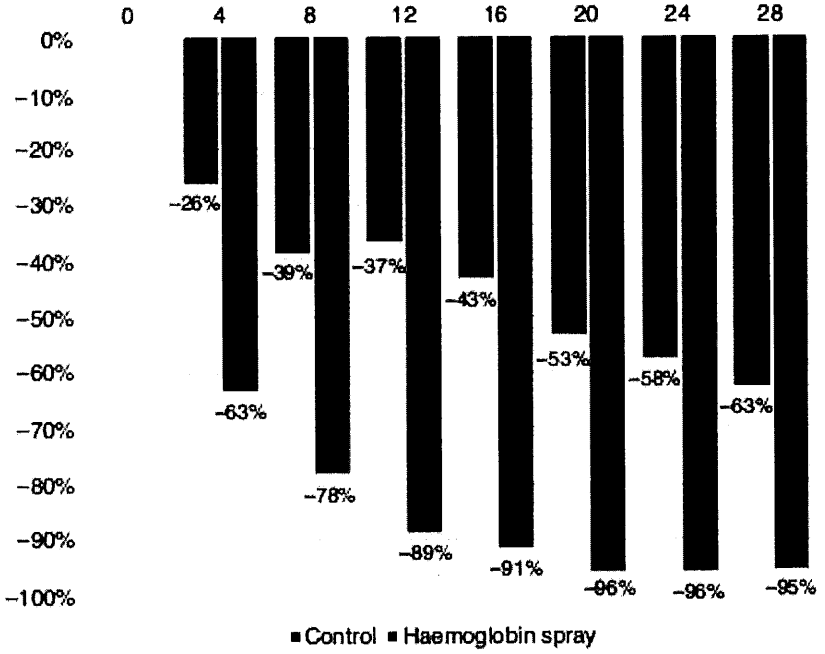
	Annual incidence	Cost per patient	Annual NHS cost (2005–2006)
Venous leg ulcers	108,600	£1,500–1,800	£168–198m
Foot ulcers	57,000	£5,200	£300m
Pressure ulcers	410,000	£4,300–6,400	£1.8–2.6bn
TOTAL	575,600	£4,000–5,400	£2.3–3.1bn

To further illustrate the point concerning the impact of foot ulcers: the healing rate of DFUs is poor; on average, 24% of wounds have healed by week 12 of treatment, and only 31% at 20 weeks of treatment (Margolis, 1999). A cohort study involving 31 diabetic patients determined that the average healing time for neuropathic DFUs is 78 days whereas this increases to 133 days for patients with additional peripheral vascular disease (Zimny et al, 2002). Further analysis has shown that the size of the ulcer negatively correlates to the healing rate, whereas a patient's age, sex, or type of diabetes is not associated with a change in healing rate outcome (Oyibo, 2001). DFU healing progress at 4 weeks of treatment is a predictor of the likelihood that the wound will be healed by 12 weeks of treatment. If the wound has not healed by at least 50% after 4 weeks, the likelihood that the DFU will be completely healed by 12 weeks is reduced to circa 10% (Sheehan, 2003). Taken together, there is a major group of patients with DFU -those with larger ulcers, and co-morbidities, responding poorly to standard treatment in the first 4 weeks – that is at risk of ending up with long-term wounds taking over 3 months to heal, if at all.

Oxygen is an essential component of the wound healing process (Hunt et al, 1969). Poor circulation due to diabetic angiopathy impairs the healing process and limits the degree of required growth factor release and angiogenesis (Falanga, 2005; Mathieu et al, 2006). Increasing oxygen levels can be achieved in various ways, including hyperbaric chamber treatment (Faglia, 1996). However, this method is costly, cumbersome and logistically challenging. A novel haemoglobin spray that is designed to enhance wound healing, including non-diabetic foot ulcers and DFUs, by enriching the wound area with oxygen using porcine haemoglobin is now available in the UK. The product is called Granulox and it marketed by InFirst Healthcare Ltd. The mode of action is the application of porcine haemoglobin onto a wound to facilitate increase oxygen levels through diffusion into the wound area (Arenberger et al, 2011; Norris, 2014; Hunt & Elg, 2016). Hunt & Elg, in a study with retrospective analysis of standard care DFUs and prospective assessment of Granulox adjunct therapy DFUs, have shown that the healing rate for chronic wounds is much accelerated with haemoglobin treatment. Figure 1 summarises their data.

The aim of this randomised, controlled, prospective clinical trial is to determine the efficacy of the Granulox haemoglobin spray device as an adjuvant therapy for foot ulcers, with a primary outcome measure of DFU healing at 12 weeks of treatment. The rationale behind including both diabetic and non-diabetic foot wounds is that the mechanism of action of Granulox is not affected by a patient's diabetes status and the product has shown promise in non-diabetic wounds (Arenberger et al, 2011).

Figure 1, Hunt & Elg data, DFU healing by week vs baseline.



3. INVESTIGATIONAL DEVICE

Granulox® Medical device. Class III, CE 0482

Indications: Granulox® is a spray for use on chronic wounds. Granulox® is an innovative medical device for the proposed treatment of chronic wounds, such as venous leg ulcer, arterial leg ulcer, mixed leg ulcer, diabetic foot ulcers, secondary healing of surgical wounds and pressure sores. Granulox® can also be used on sloughy and infected wounds. Each canister contains 12 ml of spray, sufficient for 30 wound treatments.

Medical Device management

The Granulox devices, ie the individual canisters, will be stored and used in line with published guidelines. Link: http://www.woundcarehandbook.com/product/2736/granulox . The stock of Granulox devices will be registered on a device log and given a local ID. Each time a canister is issued / used, this is updated on the device log. Each participant will have their own Granulox canister, to avoid any risk of cross-contamination.

A temperature-monitored refrigerator will be used for storage of the devices. The temperature will be recorded every day. Once a patient is recruited and they are treated on location - eg a community clinic away from where the pharmacy department is located, then the canister will be stored in a lockable fridge at the relevant location. These fridges on location will be monitored every 2 weeks since the product can be stored up to 6 weeks at room temperature (< 50°C).

Used canisters will be disposed of in line with local guidelines on disposal of clinical waste.

Figure 2. Granulox device

4. STUDY HYPOTHESIS

4.1 Primary objective

- To assess the efficacy of Granulox haemoglobin spray adjuvant treatment for enhancement of healing of foot ulcers when compared with standard care.

4.2 Secondary objective

- To assess any changes observed in clinical assessments, safety of Granulox, and patient-reported outcomes related to foot ulcers (including pain, mobility, quality of life)

5. STUDY PROTOCOL

5.1 Study design and timeline

This concerns a single centre, controlled prospective randomized study. The study will be carried out in Cumbria by NHS Cumbria Partnership NHS Foundation Trust. The study will take place in a local community setting with support and oversight from a GP, podiatrists and research staff. Research delivery staff will be delegated to provide support with data collection and processing.

Table 2. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
June-17	Submission for HRA approval			
July-17	NIHR portfolio adoption			
Aug-17	HRA and Trust approval	Start recruitment		
Jan-19		Finish recruitment		
Apr-19			Follow-up complete; Analyse data	
May-19				manuscript & report writing complete

5.2 Participant identification and research setting

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

The podiatry team in West Cumbria will be supporting this study, and the study will take place in Whitehaven, Workington, Cockermouth and Wigton. All research activity and also treatment as usual (ie application of dressings) will take place in these clinic settings. Additional resource, paid for by the research grant for this study, means that there is sufficient capacity to treat study participants with the Granulox medical device. All podiatrists – 4 staff in total - will receive training on the use of the medical device by a representative of InFirst Healthcare.

To summarise, the podiatrists will:

- Identify potentially eligible patients and ask verbal consent for them beign approached about the study by a member of the R&D team
- Complete the incl/excl criteria part of the screening form
- Apart from treatment as usual activities (dressings, cleaning of wound, footwear advice), measure the wound size and complete the PUSH and Texas University score once a patient has consented to taking part (informed consent will be taken by members of R&D team, or one of the podiatrist so long as GCP training has been completed).

5.3 Consent

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

Patients are also allowed to consent to taking part when first approached as long as the study has been discussed with the patient and they have been given time to read the patient information leaflet and opportunity to ask any questions that they may have. Participants will receive no incentives and consent will be regarded as a process and not a one-off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard of care will not be affected by either declining to participate in the study or withdrawing during participation. Data collected up to the date of withdrawal will be retained for analysis.

5.4 Recruitment

Participants will be randomised to either the control group (TaU) or the intervention group (TaU plus administration of Granulox spray) for 12 weeks or until ulcer healing has been achieved. All participants will have demographic data obtained and the following base line measures (table 2):

- Foot ulcer size measured with Convatec grid tool or equivalent measuring tool
- PUSH score (size and characteristics)
- Texas University grading scores.
- Mobility score (LifeSpace questionnaire)
- Quality of life assessment using
    - EQ-5D-5L
    - Cardiff Wound Impact Questionnaire
    - VAS pain scale

Table 3. Overview of measurements

Weeks	-2	0	3	6*	9*	12#	18#
Ulcer size (Convatec grid)	X	X	X	X	X	X	
PUSH score	X	X	X	X	X	X	
Texas Univ grading score	X	X	X	X	X	X	
Wound healed status		X	X	X	X	X	X
Life Space Questionnaire		X		X		X	
QoL EQ-5D-5L		X		X		X	
QoL CWIQ		X		X		X	
VAS pain scale	X	X	X	X	X	X	
Patient experience questionnaire						X@	

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

 # Allowed to be up to 2 weeks early or late

@Granulox arm participants only

The Pressure Ulcer Scale for Healing (PUSH) tool, see Appendix 1 is a standardised method of assessing and monitoring the severity and healing of both pressure ulcers and venous leg ulcers (Stotts et al, 2001; Ratliff & Rodeheaver 2005). The Pressure Ulcer Scale for Healing (PUSH) is a valid, responsive, evaluative tool to monitor and document wound progress of foot ulcers (Hon, 2010). Findings also suggest that total PUSH scores predict time-to-heal for foot ulcers (Gardner 2011).

A mobility measure will be taken using a life space questionnaire, see Appendix 1 (Stalvey *et al* 1999). This is a tool that has demonstrated reliability and construct and criterion validity in establishing the spatial extent of an older person's mobility within their home setting. There are other versions (Peel *et al* 2005) that additionally measure the use of aids and equipment however this is not of particular interest within the study, hence the simpler version will be used.

A recent review of specific health related quality of life instruments for venous leg ulcers favours the Charing Cross Venous Leg Ulcer Questionnaire (Appendix 2) (Smith *et al* 2010) above others such as the Hyland for its disease specific psychometric characteristics (Gonzalez & Verdu 2011).

5.5 Follow-up

Patients are in the study for a period of 18 weeks. Thereafter, the patient will be followed up as they would be in normal clinical practice. During and after the trial, clinical staff will redress the wound as per routine care, and during the trial they will conduct the measurement of the foot ulcer (grid measurement tool, Texas Univ grading and PUSH score). The researcher will be in attendance at -2 weeks, 0 weeks, and weeks 3,6,9,12 of study participation to randomise the patient, issue the Granulox spray if indicated, and conduct/collect the study participant questionnaires. The researcher will phone the participant at week 18 to check on wound status and any adverse event reporting.

5.6 Outcome measures

5.6.1 Primary outcome measures

The primary outcome for this trial will be the efficacy of the Granulox spray in terms of wound healing.

- Foot ulcer size, measured with Convatec grid tool (week -2, 0, 3, 6, 9, 12)

5.6.2 Secondary outcome measures

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

- Size and characteristics of foot ulcer, determined with PUSH score (week -2, 0, 3, 6, 9, 12)
- Grading of foot ulcer, using Texas Univ grading score (week -2, 0, 3, 6, 9, 12).
- Wound closure status (week 0, 3, 6, 9, 12)

- Mobility score, as determined by LifeSpace questionnaire (week 0, 6, 12)

- Visual Analogue Pain score (week -2, 0, 3, 6, 9, 12)
- Quality of life score, determined with EQ5D-5L and Charing Cross Venous Ulcer Questionnaire (week 0, 6, 12)

- Wound status check [healed, not healed, recurrence] and any incidences of adverse events (week 18)

- Patient withdrawal rates due to change in management (e.g. need for surgery)
- Wound infection rates, any other adverse events
- Patient experience and satisfaction with the Granulox product and treatment regime

6. SUBJECTS

6.1 Anticipated number of research subjects

There is pilot data to base a *priori* sample size calculation on, but this concerns a single retrospective study (Hunt and Elg, 2016). In their study, they observed 37% (control) and 89% (Granulox) wound size change versus baseline measurement at 12 weeks. This would mean that 14 patients (7 in each arm) would be sufficient to have the trial powered to 80%. For this present trial, a more conservative approach is taken, see Table 4. The earlier published average healing rate of 25% is used as the anticipated minimum healing rate (Margolis, 1999). Since some patients may require surgical intervention or may withdraw, a hypothetical 20% dropout rate is calculated into the sample size (actual attrition rate is a study objective). A theoretical 1:1 allocation to the control and Granulox intervention group respectively will be applied. However, because the PUSH score is not known beforehand this may not be achieved if more patients are recruited into one of the two PUSH cohorts. Diabetic foot ulcers (DFUs) and other foot ulcers will be randomised from separate randomisation lists.

The primary outcome, average percentage decrease in ulcer size between baseline and 12 week follow-up is used for sample size calculation. Power calculations for sample size, 80% power and 5% significance, based on two-sided Mann-Whitney U-test. A priori power calculations using GPower 3.1 software, result in the following sample size summarized in Table 4. This is based on the DFU study by Hunt and Elg. A further 20 patients with non-diabetic foot ulcers will be recruited to pilot what impact Granulox has on those types of wounds.

Table 4, Sample size calculation

	Median change in DFU ulcer size at 12 weeks (presume decrease for both arms, ie one-tailed approach)	**Standard Deviation**
Arm A (*hypothetical*)	*52%*	*30%*
Arm B (*hypothetical*)	*25%*	*30%*
	Power beta of 80%, Alpha p-value of 0.05, Effect size 0.9 Sample size required without any drop-out: 34 samples.	

	Sample size with 20% attrition rate included: 40 **Total of 40 DFU patients:** - **20 Patients to receive treatment as usual (TaU)** - **20 Patient to receive TaU plus Granulox spray** **Plus 20 non-DFU foot ulcers:** - **10 Patients to receive treatment as usual (TaU)** - **10 Patient to receive TaU plus Granulox spray**

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

The calculation does take into account a 10% patient attrition rate (withdrawal and loss to follow-up), since this involves a study with at least two visits. Patients will be recruited from the adult (age 18+) population routinely seen by the evaluating clinical staff members.

6.1.1 Randomisation

Following written consent at -2 weeks, participants will be observed for two weeks to establish healing rate. At the end of two weeks, patients are only eligible for the intervention phase if their wound has healed <50% in the preceding two weeks. At this point, week 0, participants are allocated at random to the control or Granulox intervention group, using a randomised sequence from the freeware randomisation programme, see https://www.randomizer.org/ . The randomisation is stratified for ulcer size, with PUSH score of 5 or less, and 6 or above as the cut-off. This size has been determined as the average size of a presenting foot ulcer previously (Zimny et al, 2002).

Sequential envelopes with each next randomisation allocation will be used to achieve concealment and these will be kept in the research department. The researcher will then inform the regular healthcare professional for the participant in question, and the participant themselves, which treatment they've been allocated to. The researcher will dispatch a Granulox canister to the clinic where the participant will be seen. At this stage the twice weekly treatment (though three applications per week would be allowed if dressing change is more than twice a week) will commence.

As the study involves administration of a spray it is not possible to achieve blinding for the participants nor the researchers – it is recognised that this increases the risk of bias.

6.2 Eligibility criteria

The criteria outlined here are to enter the study, ie the screening phase.

6.2.1 Inclusion criteria

- Clinical diagnosis of a Foot Ulcer, present on area that is measurable with a grid sheet (this can include plantar, calcaneus, dorsal, hallux, apex, or ankle based ulcers). This includes DFU, peripheral arterial disease related wound, or other aetiology.
- Foot ulcer present for at least 2 weeks.
- Adult patients aged > 18 years
- Patients with recurrent wounds, including multiple wounds, are eligible. The largest of the wounds, that is measurable with a grid sheet, will be selected for the trial.
- Mental capacity to give consent

6.2.2 Exclusion criteria

- Under the age of 18 years
- Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity
- Limited life expectancy, i.e. undergoing palliative care
- Active infection in foot ulcer that cannot be managed in podiatry service (ie requires specialist secondary care intervention)
-
- Any personal objection to being administered a product containing porcine material.
- Patients who are participating in another research study involving an investigational product.
- The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives, including alcohol or drug dependency.
- Foot ulcer in area of the foot, e.g. in between toes, which would make exact ulcer size measurement impossible.
- Patient pregnant, actively planning to become pregnant, or lactating
- Ankle brachial index < 0.6, measured within 3 months of baseline visit

6.3 Early withdrawal of subjects

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

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

7. SAFETY

7.1 Potential risks & benefits to study participants

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

For the participants in the control group there is no direct benefit in taking part in this study. They will be cared for in exactly the same manner as they normally would. For participants in the Granulox intervention group, there may be benefits in terms of improved foot ulcer healing compared to normal standard care. Although there is initial evidence that this is indeed the case, this has not yet been proven and established through a prospective randomised trial, and this study is aimed to assess this. Participants cannot claim payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

7.2 Safety definitions

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

7.3 Procedures for recording adverse events

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

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

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

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

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

8. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN

8.1 Analysis of baseline characteristics

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

- Age
- Gender
- BMI
- Smoking status
- Significant comorbidities, including peripheral arterial disease, heart failure, pretibial oedema.
- Aetiology and location of wound
- Presence of diabetes, and if so length of having condition
- Neuropathy
- Offloading of the foot ulcer
- Ankle-Brachial Index value (measured within last 3 months)
- Wound infection or not (or infected at any stage of participation)

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

8.2 Primary outcome statistics

The primary objective for this trial is the healing rate of the foot ulcers, as assessed by tracing the wound using a Convatec measuring grid, or an equivalent measuring grid tool.

The average difference between time points will be calculated per group, 12 weeks being the primary endpoint but weeks 3, 6 and 9 will also be analysed. To compare the groups, the Mann-Whitney U-test will be applied.

8.3 Secondary outcome statistics

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

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

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

To evaluate the wider effects of Granulox treatment on foot ulcer healing compared to the control group, the following parameters will be compared at week 3, 6, 9 and 12 weeks:

- PUSH score
- Texas Univ grading score
- Mobility score
- Ankle range of motion
- Visual analogue pain score
- EQ5-5D-5L score
- CWIQ score

To compare the groups, Mann-Whitney U-test will be applied.

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

9. DATA HANDLING AND MONITORING

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

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

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

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

10. GOVERANCE OF STUDY

10.1 Approvals

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

10.2 Sponsor & Indemnity

Cumbria Partnership NHS Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. InFirst Ltd has provided a grant for this study by means of provision of the Granulox spray free of charge and a grant worth £6370..

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

11. PUBLICATION AND DATA-SHARING POLICY

The study will be registered on ISRCTN or Clinical Trials Gov website, in line with CONSORT guidelines on good practice in clinical research.

The results of this study will potentially be disseminated through:

- Peer-reviewed manuscript in scientific journal

- Internal report to the funder of the trial, InFirst

As stated in Section 9 and the PIL and ICF, anonymised study data will be shared with InFirst as part of the research grant agreement.

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

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APPENDIX 1. TOOLS AND ASSESSMENTS

This appendix contains:

- The PUSH tool that will be used to assess each leg ulcer at -2, 0, 3, 6, 9 and 12 weeks (from Stotts et al, 2001)
- Texas University ulcer grading score at -2, 0, 3, 6, 9 and 12 weeks (from Armstrong et al, 1998)
- The mobility life space questionnaire that will be completed for each participant to confirm limited mobility at 0, 6, and 12 weeks (from Stalvey et al 1999)
- The EQ-5D-5L Questionnaire used to score generic quality of life for each participant at 0, 6, and 12 weeks
- The Cardiff Wound Impact Questionnaire used to score wound-related quality of life for each participant at 0, 6, and 12 weeks (from Price & Harding, 2004) – *see separate document*
- Visual analogue pain scale at -2, 0, 3, 6, 9 and 12 weeks

NATIONAL PRESSURE ULCER ADVISORY PANEL

Pressure Ulcer Scale for Healing (PUSH)
PUSH Tool 3.0

Patient Name_____ Patient ID# _____

Ulcer Location _____ Date _____

Directions:

Observe and measure the pressure ulcer. Categorize the ulcer with respect to surface area, exudate, and type of wound tissue. Record a sub-score for each of these ulcer characteristics. Add the sub-scores to obtain the total score. A comparison of total scores measured over time provides an indication of the improvement or deterioration in pressure ulcer healing.

LENGTH X WIDTH (in cm^2)	**0** 0	**1** < 0.3	**2** 0.3 – 0.6	**3** 0.7 – 1.0	**4** 1.1 – 2.0	**5** 2.1 – 3.0	**Sub-score**
		6 3.1 – 4.0	**7** 4.1 – 8.0	**8** 8.1 – 12.0	**9** 12.1 – 24.0	**10** > 24.0	
EXUDATE AMOUNT	**0** None	**1** Light	**2** Moderate	**3** Heavy			**Sub-score**
TISSUE TYPE	**0** Closed	**1** Epithelial Tissue	**2** Granulation Tissue	**3** Slough	**4** Necrotic Tissue		**Sub-score**
							TOTAL SCORE

Texas University grading score

University of Texas Diabetic Wound Classification Diabetes Care 1998; 21: 855-859

Stage	Grade			
	0	1	2	3
A	Pre or post lesion – intact	Superficial wound	Penetrating to tendon or capsule	Penetrating to bone or joint
B	+Infection	+Infection	+Infection	+Infection
C	+Ischaemia	+Ischaemia	+Ischaemia	+Ischaemia
D	+Infection and ischaemia	+Infection and ischaemia	+Infection and ischaemia	+Infection and ischaemia

Life Space Questionnaire

Interviewer: "I am interested in all the places that you have been within the last 2 weeks"

1. During the past 2 weeks have you been to other rooms of your home besides the room where you sleep?

   1 = ...Yes 2= .....No ☐

2. During the past 2 weeks have you been to an area immediately outside your home, such as your porch, patio, garage?

   1 = ...Yes 2= .....No ☐

3. During the past 2 weeks have you been to an area outside your home such as a yard, courtyard, garden, driveway?

   1 = ...Yes 2= .....No ☐

4. During the past 2 weeks have you been to places in your immediate neighbourhood but beyond your own property?

   1 = ...Yes 2= .....No ☐

5. During the past 2 weeks have you been to places outside your immediate neighbourhood but within your town or community?

   1 = ...Yes 2= .....No ☐

6. During the past 2 weeks have you been to places outside your immediate town or community?

   1 = ...Yes 2= .....No ☐

7. During the past 2 weeks have you been to places outside of Cumbria?

   1 = ...Yes 2= .....No ☐

EQ-5D-5L

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

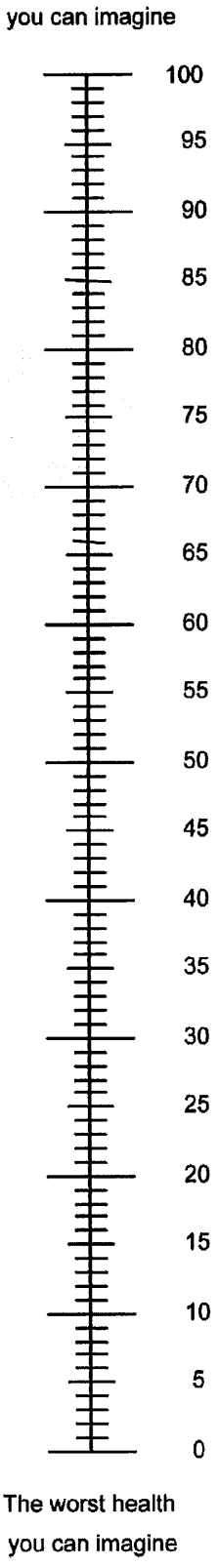
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

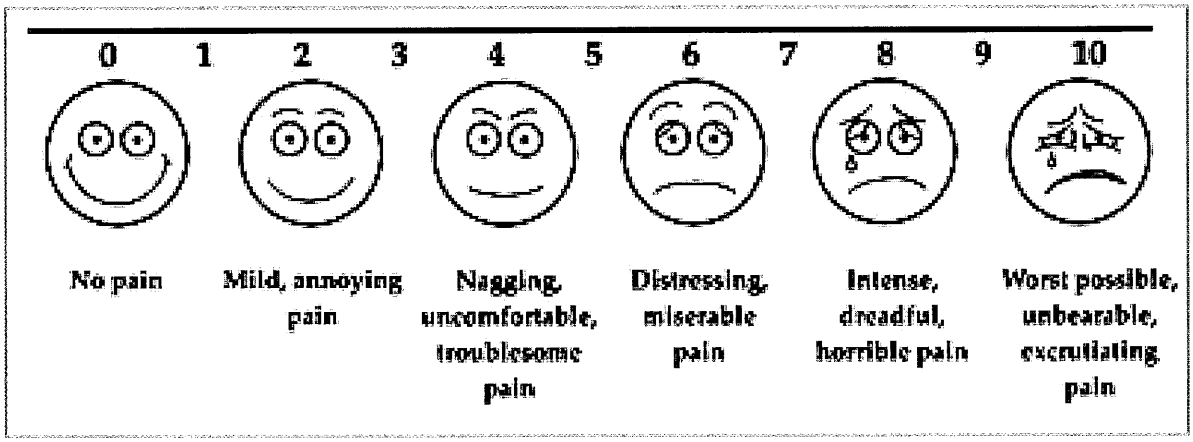
- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

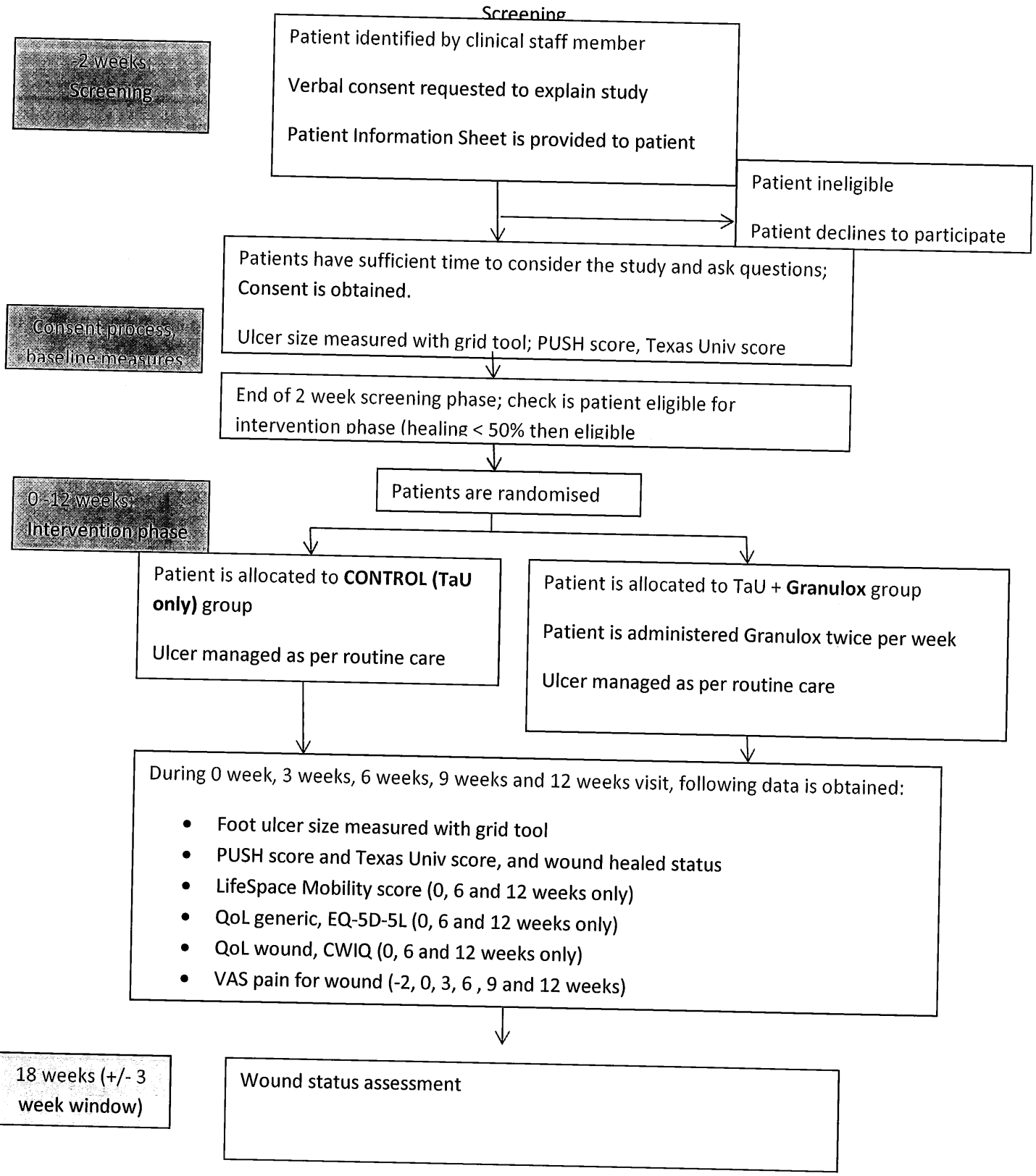


Visual analogue Pain score

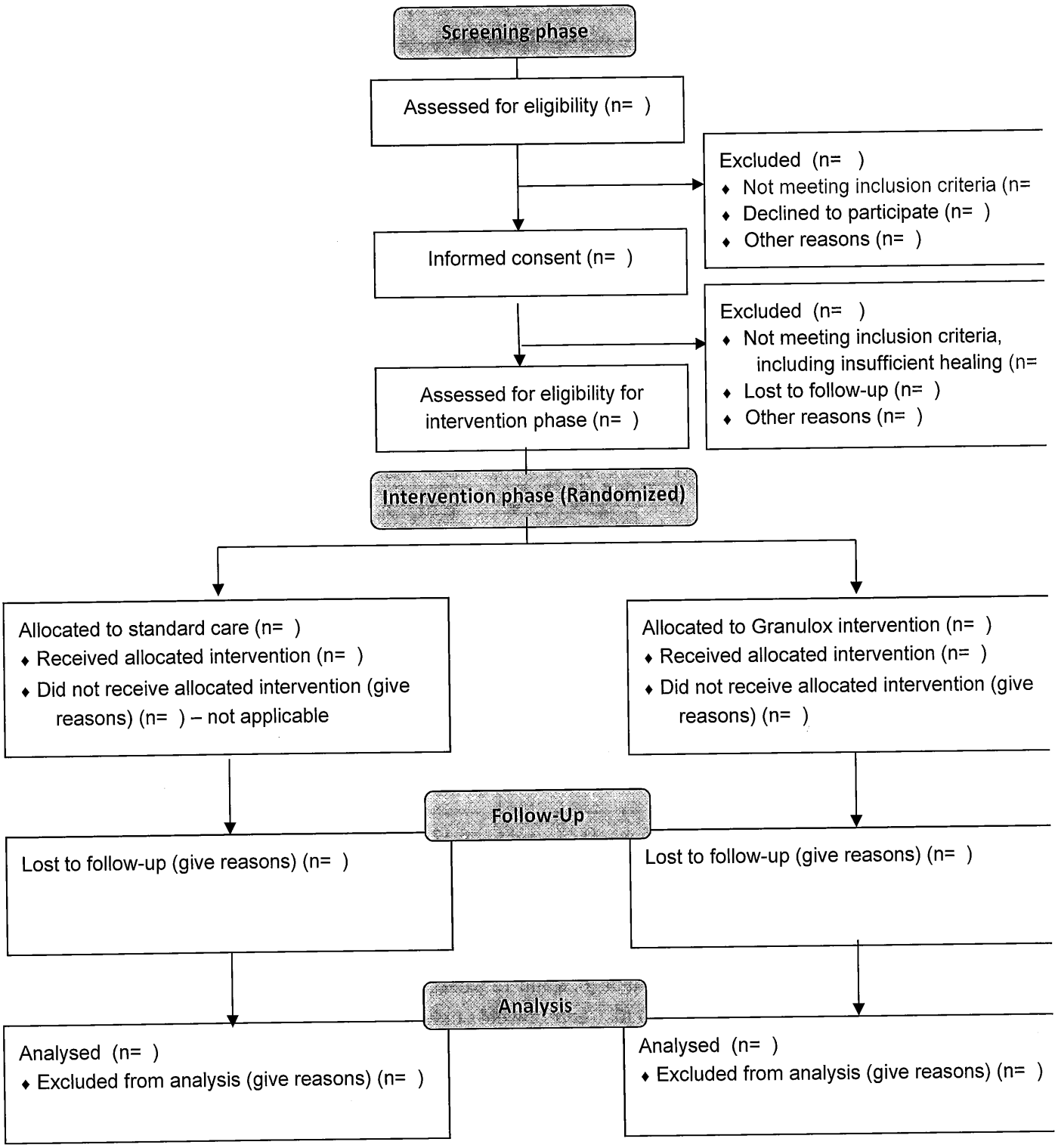
How painful has the foot ulcer (that we are treating in the research trial) been in the last week:



Please put a vertical line on the numbered bar above


-2 weeks: Screening
Screening
Patient identified by clinical staff member
Verbal consent requested to explain study
Patient Information Sheet is provided to patient
Patient ineligible
Patient declines to participate
Consent process, baseline measures
Patients have sufficient time to consider the study and ask questions; Consent is obtained.
Ulcer size measured with grid tool; PUSH score, Texas Univ score
End of 2 week screening phase; check is patient eligible for intervention phase (healing < 50% then eligible
0 -12 weeks: Intervention phase
Patients are randomised
Patient is allocated to CONTROL (TaU only) group
Ulcer managed as per routine care
Patient is allocated to TaU + Granulox group
Patient is administered Granulox twice per week
Ulcer managed as per routine care
During 0 week, 3 weeks, 6 weeks, 9 weeks and 12 weeks visit, following data is obtained:
Foot ulcer size measured with grid tool
PUSH score and Texas Univ score, and wound healed status
LifeSpace Mobility score (0, 6 and 12 weeks only)
QoL generic, EQ-5D-5L (0, 6 and 12 weeks only)
QoL wound, CWIQ (0, 6 and 12 weeks only)
VAS pain for wound (-2, 0, 3, 6 , 9 and 12 weeks)
18 weeks (+/- 3 week window)
Wound status assessment

APPENDIX 3. CONSORT FLOWCHART



**Based on CONSORT Flowchart*