North Cumbria Integrated Care NHS Foundation Trust

ANODE

Assessment of Natrox Oxygen DElivery

Prospective, multicentre, randomised controlled feasibility trial of the application of NATROX® topical oxygen therapy in patients with chronic and delayed healing foot ulcers.

Version 5.1, dd 14Jan2022

Chief Investigator's Statement of Ownership and Content.

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

Name (PRINT):_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE:	Prospective, multicentre, randomised controlled feasibility trial of the application of NATROX® topical oxygen therapy in patients with chronic and delayed healing foot ulcers.
Short title:	ANODE study, Assessment of Natrox Oxygen DElivery
IRAS number	262187
Device description	The NATROX® oxygen wound therapy device is a battery-operated class II medical device licensed under Medical Device Directive 93/42/EEC. The 'box' contains the electrolysis-based oxygen generator and chargeable battery, and this is connected to the oxygen delivery system, a 'web' shaped applicator connected via a tube. In this manner 98% pure oxygen is supplied to the wound. The rate achieved is approximately 15 ml per hour. The web is placed on the wound and dressing is placed over it, and the device is then worn 24/7 by the patient.
Study design	Prospective, multi-centre, randomised controlled feasibility trial
Primary objective / outcome measures	To assess the feasibility of conducting a full RCT in the future - Participants' experience of and compliance with Natrox oxygen therapy - Recruitment and attrition rates, willingness of patients to consent and to be randomised, response rates to questionnaires, and degrees of missing data - Testing of eligibility criteria and ability/willingness of clinical staff to partake in recruitment and follow-up of participants - Adequacy of duration of follow-up (e.g. in relation to foot ulcer healing) - Appropriateness of inclusion/exclusion criteria and outcomes measures (both clinical and patient-reported).
Secondary objectives / outcome measures	Descriptive assessment of wound size and characteristics (wk 0,3,6,9,12). - Percentage 'wound healed' vs week 0. - Percentage healing of the wound vs week 0. - Change in semi-quantitative PUSH ulcer size score vs week 0 - SINBAD score (DFU only) vs week 0 - Wound closure status - Clinical characterisation of wound (erythema, purulence, odour, patient-reported pain) Safety of applied oxygen therapy in comparison to standard care arm (ongoing): - Wound infection incidence - Need for secondary interventions, such as surgery

	Patient-reported outcome measures (wk 0, 6, 12) - (Wound related) Quality of life scores (EQ-5D-5L and CWIQ) - Wound pain scale
Patient population	A total of 24 eligible participants will be randomised to receive either standard care or standard care plus Natrox topical oxygen therapy. Patients to be aged eighteen or over, with measurable foot ulcer present for at least two weeks, treated in podiatry clinic. Participants must have the capacity to provide informed written consent and complete patient reported outcome measures, and be willing and capable to wear the Natrox device. All participating patients – whose index wound has not healed by 50% or more in first four weeks of screening whilst in the study and under care of podiatry team - will be randomised for the trial phase. Those patients who were enrolled and whose foot ulcer healed 50% or more complete the study at the end of the four-week screening phase. In summary, of those participants whose wound does not heal 50% in four-week screening phase: - 12 Patient will receive treatment as usual (TaU) - 12 Patients will receive TaU plus adjunct Natrox topical oxygen therapy Randomisation will be stratified for ulcer size, with cut-off PUSH score of up to and including 5, and 6 and above.
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
Research grant provider	Inotec AMD Limited Ground Floor, Unit 7340 Building 7300, Cambridge Research Park Waterbeach, Cambridge, CB25 9PD, UK T: +44 (0) 1223 661830 E: nick.howard@natroxwoundcare.com
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Organisation where research will take place	North Cumbria Integrated Care NHS Foundation Trust Main locations: North Carlisle Medical Centre Carlisle, CA3 9JZ Plus podiatry Clinics, run by North Cumbria Integrated Care NHS Foundation Trust Trust employed podiatrists, across North Cumbria. South Tyneside NHS Foundation Trust, South Tyneside District Hospital, Harton Lane, South Shields, Tyne and Wear, NE34 0PL. And associated podiatry clinics.
Planned timeline	Recruitment start date (first patient, first visit): 10 October 2019, Recruitment end date (last patient, first visit): 31 July 2022 Study completion date (last patient, last visit): 30 Nov 2022 Trial end date: 31 Dec 2022
Protocol version, date	Version 5.1, dd 14 January 2022

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1. LAY SUMMARY

Foot ulcers, which includes diabetic foot ulcers (DFU), can lead to infection and further deterioration to health. They are a considerable burden to both the NHS and the patient. The management of foot ulcers initially focuses on achieving wound healing. However, in many cases this objective is not met and chronic wound management then shifts its attention to avoiding infection and further complications. Clinicians have the option to treat the wound conservatively or more aggressively with oxygen. At present there is a lack of data available to aid clinicians in deciding what approach is best. The NATROX® oxygen wound therapy device is a licensed battery-operated class II medical device. The 'box' contains the electrolysis-based oxygen generator and chargeable battery, and this is connected to the oxygen delivery 'web' shaped applicator via a tube. The rate achieved is approximately 15 ml per hour. The web is placed on the wound and dressing is placed over it. In comparison to a spray or chamber, the Natrox system is portable and does not alter the frequency of clinical care required. Thus far, published data suggests that the Natrox device is capable of healing chronic delayed-healing foot wounds, typically present for over a year, by more than 50% over a treatment period of 8 weeks.

There are a few papers published on the use of and outcomes with the Natrox device in chronic foot ulcer patients, totalling circa 150 patients. However, there is a lack of evidence on how the device is perceived by patients who use it, i.e. acceptability of the device, and compliance rates. From a clinical perspective, more information is indicated to determine if, and how, wounds change in terms of bioburden (the microbiologic make-up of the wounds) as this may have implications if infection occurs in ulcers treated with Natrox. Finally, the effectiveness of Natrox needs to be evaluated in a randomised controlled trial setting.

In this feasibility trial, twenty-four patients, recruited from two NHS Trusts, will be enrolled in a randomised controlled trial. Participants will be eligible for randomisation to standard care or standard care plus adjunct Natrox oxygen therapy if their wound has not healed by at least 50% in the four weeks prior. In the trial phase, clinical (wound status) and patient-reported outcome measures will be collated at baseline, and periodically up to 12 weeks. Since this concerns a feasibility trial, the acceptability of the device, compliance with the therapy and study recruitment and retention rates will be assessed.

Since the Natrox device is already CE-marked, it can be incorporated in standard wound care practice across the UK without the need for regulatory delays and with minimal need for staff training. However, this is provided Natrox proves to be effective, safe, and cost-effective.

2. INTRODUCTION

The occurrence of foot ulcers has enormous cost complications. Figures available for diabetic foot ulcers (DFU) alone total £650 million per year once associated morbidity is taken into account (NHS Diabetes report). In the UK alone, 169,000 diabetic foot ulcers (DFU) occur every year (Guest et al, 2015). The International Diabetes Federation (2005) reported that up to 70% of all leg amputations happen to people with diabetes and 85% are preceded by a foot ulcer. Furthermore, three quarters of diabetics who experience an amputation will die within five years (Schofield *et al,* 2006). Diabetes NHS (2012) estimates total National Health Service (NHS) spending on ulceration and amputation in people with diabetes in England in 2010/11 was circa 0.7% of the budget and warned as diabetic numbers grow so will this expenditure. Lipsky *et al* (2004, 2012) associated infection in DFU with high mortality, high attendance at clinics and possible risk of amputation, advising antibiotics are required for infected wounds, but there is no evidence to support issuing antibiotics for uninfected ulcers. This is a critically important topic, since the longer that healing is delayed, the higher the risk of infection developing (Hampton and Collins, 2005; Grothier, 2015). 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. Therefore, enhancement of foot ulcer healing rate is desirable to minimise morbidity and healthcare costs.

Each year, the NHS spends approximately £2.3bn – £3.1bn (at 2005-2006 cost) on dressings and associated products, equating to 3% of the total estimated health expenditure (Posnett and Franks, 2008). Furthermore, patients with wounds cost the NHS up to £5 billion more per annum than matched control patients (Guest et al, 2015). Regarding dressing prescriptions, silver dressings represent one seventh of wound dressing prescriptions (Iheanado, 2010), resulting in a high cost implication for the NHS. Alternative approaches to accelerating the healing rate of DFUs may be beneficial not only from a patient perspective, but also in terms of reducing healthcare costs.

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. An alternative is a porcine haemoglobin, Granulox, has shown initial promise but is derived from animals and needs to be applied numerous times per week in spray form (Arenberger et al, 2011; Norris, 2014; Hunt & Elg, 2016). The newly developed Natrox topical oxygen therapy device takes a different approach. It uses an electricity-

based oxygen generator, which then feeds oxygen through a tube and a 'web' onto the wound area (see Figure 1 and https://www.natroxwoundcare.com/). An initial pilot study on 10 chronic DFU wounds has shown promise; a median healing rate of 53% was achieved after eight-week long treatment with Natrox (Hayes et al, 2017). Similar results were achieved with a larger cohort of varying types of chronic wounds, including DFUs, venous leg ulcers, and arterial leg ulcers (Kaufman et al , 2018). The aim of this randomised, controlled, prospective clinical trial is to determine if the device is acceptable and feasible to introduce into foot ulcer treatment. Furthermore, the methodology applied in this initial study will be appraised for suitability in a larger trial setting. As a secondary objective, the efficacy of the Natrox topical oxygen therapy device as an adjunct therapy for foot ulcers will be assessed. The rationale behind including both diabetic and non-diabetic foot wounds is that the mechanism of action of Natrox is not affected by a patient's diabetes status and the product has shown promise in non-diabetic wounds (Kaufman et al, 2018).

3. INVESTIGATIONAL DEVICE

3.1 Introduction Natrox device

The Natrox® topical oxygen therapy device is a class II medical device licensed under Medical Device Directive 93/42/EEC. The system has two elements, namely the ; the Natrox® Oxygen Generator and the Natrox® Oxygen delivery system. The Natrox® generator is battery-operated and delivers 98% pure humidified oxygen to the wound bed at 13 ml/hour – oxygen is generated through water electrolysis. It is supplied with two rechargeable batteries and a charging kit. Since each battery will last for approximately 30 hours, users are advised to charge one battery whilst using the other and to change them over daily. The Natrox® oxygen delivery system is a sterile, single-use tube and 'web' that facilitates the wound interface. Due to the web design, wound exudate can escape and be absorbed by dressings without impairing the flow and diffusion of oxygen across the wound surface. The web is connected to the generator via a one meter long thin flexible tube. The Natrox® oxygen delivery system is to be changed at each dressing change in accordance with good clinical practice (it can stay in place for up to 7 days if clinically appropriate and indicated). Further information can be found at https://www.natroxwoundcare.com/ and please see paragraph below. If a patient wishes to get changed or have a shower then the oxygen delivery system can be temporarily disconnected from the oxygen generator. However, continues application of the device is indicated to achieve optimal therapy.

Figure 1, The Natrox topical oxygen therapy device

3.2 Medical Device management and staff training

The Natrox devices and related oxygen delivery systems will be stored in the podiatry clinic rooms or R&D office at the temperature and conditions recommended by the manufacturer. No requirement for involvement pharmacy or clinical trials pharmacist. Standard available stocks of dressings to be used as part of standard foot ulcer care.

The Natrox medical device will be managed as such:

- The suitably trained/delegated podiatrist will apply the Natrox device to the wound. This means both the 'web', the 'tubing' and the oxygen generating 'box'.
- Then the regular dressings will be applied, again by podiatrist (as per usual care)
- At the first study appointment, week 0, the patient will be explained how the box can be detached from the tubing/web, in order to allow patient to wash or change clothes.
- At this point, the patient must also be told to change the box every 24 hrs. The official Natrox instruction leaflet will be given to patient as an aide memoire.
- Patients must be seen in podiatry at least once every 7 days whilst they are in the trial, since the same web should not be on for longer than 7 days. This timing is in line with standard care.
- The web and tubing is replaced at this point. The replacement can take place sooner than after 7 days, if the dressing needs to be changed at that point anyway. Again, the podiatrist changes the web and tubing.
- At each clinic visit the patient is asked if they've experienced any issues with the device.

A team of podiatrists at both recruitment sites have been identified, see protocol summary pages 2-4, and they will be trained on the application and use of the Natrox device by a representative from Inotec AMD Limited. This person will also be available for any troubleshooting once the study is live. The podiatrists and research staff will also attend a site initiation visit on the ANODE study itself. For both sessions an attendance list will be circulated and signed by attending staff. All trained staff will then be added to delegation log for the ANODE study and be delegated the appropriate and relevant tasks in relation to study delivery.

4. STUDY HYPOTHESIS

4.1 Primary objective

- To assess the feasibility of conducting a full RCT in the future.

4.2 Secondary objective

- To assess the acceptability and efficacy of the Natrox oxygen therapy device as an adjuvant therapy for foot ulcer healing

5. STUDY PROTOCOL

5.1 Study design and timeline

This concerns a multi-centre, controlled prospective randomized feasibility study. The study will be carried out in Cumbria by North Cumbria Integrated Care NHS Foundation Trust and South Tyneside & Sunderland Hospital NHS Foundation Trust. The study will take place in a local community setting with support and oversight from a senior podiatrist, the wider podiatry team and research staff. Research delivery staff will be delegated to provide support with data collection and processing. Table 1 outlines the planned timeline.

Table 1. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
May-19	Submission for HRA approval			
July-19	HRA and Trust approval; NIHR portfolio adoption			
Oct-19		Start recruitment		
Jul-22		Finish recruitment		
Nov-22			Follow-up complete; Analyse data	
Dec-22				Manuscript & report writing

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 teams in Cumbria and South Tyneside will be supporting this study, and the study will take place in those localities. All research activity and also treatment as usual (ie application of dressings) will take place in these clinic settings.

To summarise, the podiatrists will:

- Identify potentially eligible patients and ask verbal consent for them being approached about the study by a member of the R&D team
- Complete the inclusion / exclusion criteria checklist on the screening form
- Treatment as usual activities (dressings, cleaning of wound, footwear advice), measure the wound size, take photos of wound, and complete the PUSH and SINBAD score once a patient has consented to taking part (informed consent will be taken by members of delegated R&D team, or one of the podiatrists as long as they are listed on the delegation log).
- Apply the Natrox device in accordance with manufacturer's instructions to suitably eligible participants.

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. If there is insufficient time in clinic, the podiatrist or delegated research can follow-up with a phone call to the patient to ensure they understand the PIS and have had opportunity to ask any questions they may have.

The start of the 4-week screening period is the date of written consent being obtained.

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. Only one questionnaire will be presented to patients who withdraw or complete early, the patient experience questionnaire (still voluntary for patients to complete or not).

5.4 Recruitment

Participants will be enrolled for a total of 16 weeks, see Table 2, or until ulcer healing has been achieved (if the latter occurs then they will still be followed up according to the study schedule in terms of patient-reported outcome measures). All participants will have demographic and medical data obtained and a number of baseline and follow-up measures.

Table 2. Overview of study measurements

Weeks	-4	0*	3*	6*	9#	12˜
Clinical characterization of wound	X	X	X	X	X	X
Ulcer size (Coloplast grid or suitable equiv)	X	X	X	X	X	X
PUSH score	X	X	X	X	X	X
SINBAD DFU grading score (DFU only)	X	X	X	X	X	X
Wound status (closed/recurrence/infection)		X	X	X	X	X
photo of wound (if possible and consented by patient)		X		X		X
QoL CWIQ		X		X		x
QoL EQ-5D-5L		X		x		X
Experience questionnaire *(Natrox only)*						X

** Up to 1 week early or late*

 # Up to 2 weeks early or late

˜Up to 3 weeks early or late (in exceptional circumstances, wk 9 and 12 visit can be combined if wk 9 visit is late and wk 12 visit can only take place early)

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

The SINBAD grading score was developed and validated for use in patients with diabetes (Ince etal, 2008).

5.5 Follow-up

Patients are in the study for a period of 16 weeks, of which 4 weeks are screening and 12 weeks are intervention or control. Thereafter, the patient will be followed up as they would be in normal clinical practice. During and after the trial, clinical staff will redress the wound as per routine care, and during the trial they will conduct the measurement of the foot ulcer (grid measurement tool, SINBAD grading and PUSH score). The researcher will be in attendance at week -4, 0, 3, 6, 9, and 12 of study participation to consent the patient and conduct/collect the study participant questionnaires.

The clinical outcomes and scores, ie characterisation of wound and SINBAD (both part of standard clinical practice), plus ulcer size and PUSH score are conducted by the treating podiatrist. Furthermore, microbiological swabbing of the wound is also performed by the podiatrist.

The patient-reported scores, wound-related quality of life score (Cardiff wound index), generic quality of life score (EQ-5D-5L) and end-of-trial experience survey (Natrox wearers only) are all competed by the patient and the researcher can support the patient if they indicate that they require some assistance (the researcher will not prompt patients to select a certain answer).

5.6 Outcome measures

5.6.1 Primary outcome measures

To assess the feasibility of conducting a full CRT in the future, the primary outcome measures are mainly:

Trial-related outcome measures

- Participants' compliance to and satisfaction with Natrox device
- Recruitment and attrition rates, willingness of patients to be consented and randomised, response rates to questionnaires, and degrees of missing data
- Testing of eligibility criteria and ability/willingness of clinical staff to partake in recruitment of participants
- Ability of sites and clinicians to recruit and randomise patients
- To assess any training requirements
- Adequacy of duration of follow-up (e.g. in relation to foot ulcer healing)
- Fitness for purpose of data collection methods including across and between care settings
- Suitability of inclusion/exclusion criteria and outcome measure tools.
- Adverse events

5.6.2 Secondary outcome measures

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

The main clinical outcome for this trial will be the efficacy of the Natrox oxygen therapy in terms of wound healing. For all participants, wound healing will be measured

Foot ulcer size, measured with wound grid tool (week -4, 0, 3, 6, 9, 12). Measured in % change in cm^2 - between week 0 and weeks, 3, 6, 9, and 12 respectively

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

- Clinical characterisation of wound (incl. erythema, purulence, odour), wound closure status
- PUSH and, if applicable, SINBAD DFU score

Extended safety outcome measures, general and in relation to applied Natrox (ongoing):

- Wound infection incidence
- Need for secondary interventions (incl. need for surgery, admission to hospital, iv antibiotics)
- (indirect) reaction to Natrox, the web itself or oxygen therapy
- Any other adverse events

Patient-reported outcome measures (wk 0, 6, 12)

- Quality of life score (EQ-5D-5L and Cardiff Wound Impact Questionnaire)

6. SUBJECTS

6.1 Anticipated number of research subjects

This concerns a feasibility trial, and therefore the results from this study should inform a potential effect size for Natrox oxygen therapy, and also the degree in variance in wound healing rates (primary clinical outcome). To date, there is not sufficient published data to gain an insight in the effect that Natrox may have on foot ulcer healing. Hayes et al (2017) previously conducted a pilot study involving 10 DFU patients. In that study, there was no screening phase and Natrox treatment lasted for eight weeks. At the week 8 time point, a mean healing vs baseline of 51% was achieved.

Guidance from a publication by Julious (2005) advises the use of 12 participants per treatment arm, and this approach will be taken here (see Table 3). Patient withdrawal rates before week 12 are not known at present and measuring this will be a primary aim

Table 3, sample size numbers required, based on hypothetical differences between published data and study outcomes

	Standard care (control) arm	**Standard care plus Natrox oxygen therapy arm**
Patients (n)	12	12

Since this concerns a randomised controlled trial, albeit in the shape of a feasibility study, reprting will be done in line with CONSORT guidelines (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 2).

Since this study involves a screening period, after which patients may not qualify for Natrox intervention, it is anticipated that more than 20 patients will be recruited. The patient attrition rate (withdrawal and loss to follow-up) will also be recorded, since this involves a study with at multiple visits, albeit incorporated into standard clinical appointments. Patients will be recruited from the adult (age 18+) population routinely seen by the evaluating clinical staff members.

6.1.1 Randomisation

Following written consent at -4 weeks, participants will be observed for four weeks to establish healing rate. At the end of four weeks, patients are only eligible for the intervention phase if their wound has healed <50% in the preceding four weeks. At this point, week 0, participants are allocated at random to the control or Natrox 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 Natrox device to the clinic where the participant will be seen. At this stage the continuous Natrox treatment (though disconnection for washing or changing of clothes is allowed) will commence.

As the study involves administration of a visible device, it is not possible to achieve blinding for the participants nor the researchers – it is recognised that this increases the risk of bias. Since the device has an indicator to show it is functioning, applying a sham device is not possible either on this occasion.

6.2 Eligibility criteria

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.
- Minimum chronicity of 2 weeks applicable for the index foot ulcer.
- 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)
- Ulcer penetrating the tendon, periosteum or bone, or a gangrenous or necrotic wound.
- Foot ulcer in area of the foot, e.g. in between toes, which would make exact ulcer size measurement, or application of the Natrox device, impossible.

- Currently receiving intravenous antibiotics, or within one week of receiving iv antibiotics (topical and oral antibiotics are not an exclusion criterion).
- Patients who are participating in another research study involving an investigational product that is related to the foot ulcer or a co-morbidity that may influence wound healing (incl. diabetes, peripheral arterial disease, or immune disorders).
- The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives, or significantly impede compliance with Natrox therapy.
- Any known reaction or hypersensitivity to the skin-facing component of the Natrox device, medical grade polyethylene.
- Ankle brachial index < 0.6, measured within 12 months of baseline visit (or recorded clinical opinion if calcification does not allow a reliable measurement).
- Use of barrier cream/ointment or honey-based dressing on the index wound itself

6.3 Subject withdrawal

6.3.1 Patient-driven early withdrawal and lost in follow-up

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. Since the study is not blinded, there is no requirement for an unblinding procedure.

6.3.2 Intervention deviation

Significant deterioration of index wound.

Clinical staff can stop Natrox treatment if they deem this to be clinically indicated. This is anticipated to be done only in cases where there is significant deterioration of the wound, not significant improvement. In cases of improvement the Natrox device is used until the wound is fully healed. The reason for discontinuing the Natrox therapy will be recorded, and participants will not be withdrawn from the study on that basis. This does not alter the study timelines and patients will continue to be followed up in accordance with planned study timepoints.

Examples are:

- Wound has become infected or critically colonised and treating podiatrist feels that intravenous antibiotics are indicated (see next paragraph).

- Deterioration in wound associated with increase in slough, which necessitates the use of a more absorbent dressing, and the Natrox device interferes with the dressing's usual mode of action.

- Deterioration in wound associated with increase in necrosis, which necessitates the use of a dressing that promotes hydration, and the Natrox device interferes with the dressing's usual mode ofaction.

- Adverse reactions to the Natrox device's 'web' element that touches the wound and surrounding skin will also be classed as a significant deterioration of the index wound in terms of subsequent wound management.

Even if Natrox therapy is discontinued, paarticipants will still be followed up at the indicated time points and asked to complete PROMs questionnaires, plus microbiology samples will be taken at the predetermined time points.

Use of intravenous antibiotics during trial

The use of topical or oral antibiotics is not an exclusion criterion and the initiation of said types of antibiotics does not necessitate withdrawal of the patient from the ANODE trial. However, the use of intravenous antibiotics specifically for the wound is an exclusion criterion. Therefore, if iv antibacterial treatment is required, the patient will be taken off Natrox treatment if they were allocated to that arm. Participants will still continue to be followed up to collate outcome measures in line with the protocol timelines. For participants in the treatment as usual arm the same approach will be taken, though there is obviously no requirement to withhold the Natrox treatment.

Study outcome measures will still be obtained where possible, in line with regular study timelines, and any reasons for Natrox therapy discontinuation will be recorded.

7. SAFETY

7.1 Potential risks & benefits to study participants

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

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

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 week of the investigator team becoming aware of them. For this purpose an AE report form is completed by the researcher and/or Chief Investigator. SAEs should be reported within one working day of becoming aware of the event, where possible. The chief investigator and sponsor should be notified via this e-mail address: research@cumbria.nhs.uk

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 the Natrox oxygen device. 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.

The participant's GP is informed of the adverse event. A copy of the adverse event form is sent to the GP along with a cover letter stipulating which patient it concerns. This will be done as soon as practically possible following completion of the AE form including causality reporting.

Pseudo-anonymised copies of all adverse events forms will be shared with Inotec AMD 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 and summarised:

- Age, Gender, Weight, Height, and BMI
- Smoking status and alcohol consumption
-
- Significant comorbidities, including peripheral arterial disease, heart failure, pretibial oedema.
- Aetiology, chronicity, and location of wound – chronicity relies on patient recall.
- Presence of diabetes, and if so length of having condition (chronicity)
- Neuropathy status, ischaemia status
- Offloading of the foot ulcer (yes/no)
- HBa1c (measured within last 6 months; only if diabetic)
- Ankle-Brachial Index value (if available and measured within last 12 months)
- Wound infection or not (or infected at any stage of participation)

8.2 Primary outcome statistics

The primary objective for this pilot study is the feasibility of conducting a larger scale randomised controlled trial. The secondary outcome statistics (on efficacy) will aid to inform the success of this pilot study and will therefore inform whether a larger scale trial is indicated. This will be based on signs of clinical effectiveness, positive patient feedback on the intervention, positive changes in foot ulcer related quality of life, recruitment to time and target, low attrition rates, minimal data queries and lack of or low number of adverse events. If the effect size of the Natrox intervention pedal is large enough, then this pilot trial may possibly provide a definitive answer concerning its clinical effectiveness.

The following descriptive statistics will be reported on:

- Number of patients screened

- Number of patients eligible/ineligible, and percentage of patients consented into the trial

- Number of patients completed the trial/discontinued (plus reasons if discontinued)

Patient feedback on the use and comfort of the Natrox device, and compliance with the prescribed therapy regime will be summarised in tabular and graph format.

8.3 Secondary outcome statistics

The clinically-related objective for this trial is the healing rate of the foot ulcers, as assessed by tracing the wound using a Coloplast measuring grid, or an equivalent performance-equal measuring tool.

The average difference between time points and baseline (week 0) 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 (data will be tested for normal distribution and if applicable, t-test will be applied).

The average change in healing at 12 weeks between the Natrox cohort and the control cohort within the study will be compared using the Mann-Whitney U-test or, if data normally distributed, t-test. Application of this analysis will depend on sample size of control cohort.

The average baseline demographics for participants in each group (Natrox and control) will be described and compared to ascertain the distribution of participants' data for: sex, age, HbA1c level, baseline wound size (cm2), PUSH score, SINBAD DFU grading score (if applicable), 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 foot ulcers: diabetes status, peripheral arterial disease, heart failure, pretibial oedema (Prompers et al, 2008)

The Chi-squared test will be applied to the above cross-tabulation to determine if there is a significant difference in distribution of treatment outcome in terms of 'status wound healed' (Natrox vs control).

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

- PUSH score
- SINBAD grading score
- Visual analogue pain score
- EQ5-5D-5L score
- CWIQ score

To compare, Mann-Whitney U-test between cohorts, since data is ordinal.

The sample size in this feasibility trial is too small to conduct Cox proportional hazards regression analysis to investigate the role of the dressing regime choice and other 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 15 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 (Inotec AMD Limited) 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 Inotec AMD Limited 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 and Funding

North Cumbria Integrated Care Partnership NHS Foundation Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. Natrox woundcare has provided a grant for this study by means of provision of the Topical Oxygen Therapy devices free of charge for the duration of the trial. Furthermore, the Academic Health Sciences Network North East and north Cumbria (AHSN NENC) has provided a monetary grant worth £6960.

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, if study is adopted onto NIHR Portfolio, in line with CONSORT guidelines on good practice in clinical research.

The results of this study will potentially be disseminated through:

- Peer-reviewed manuscript in scientific journal
- Internal report to the funders of the trial, Natrox wound care (part of Inotec AMD Limited) and Academic Health Sciences Network.

As stated in the PIL and ICF, anonymised study data will be shared with Natrox and AHSN 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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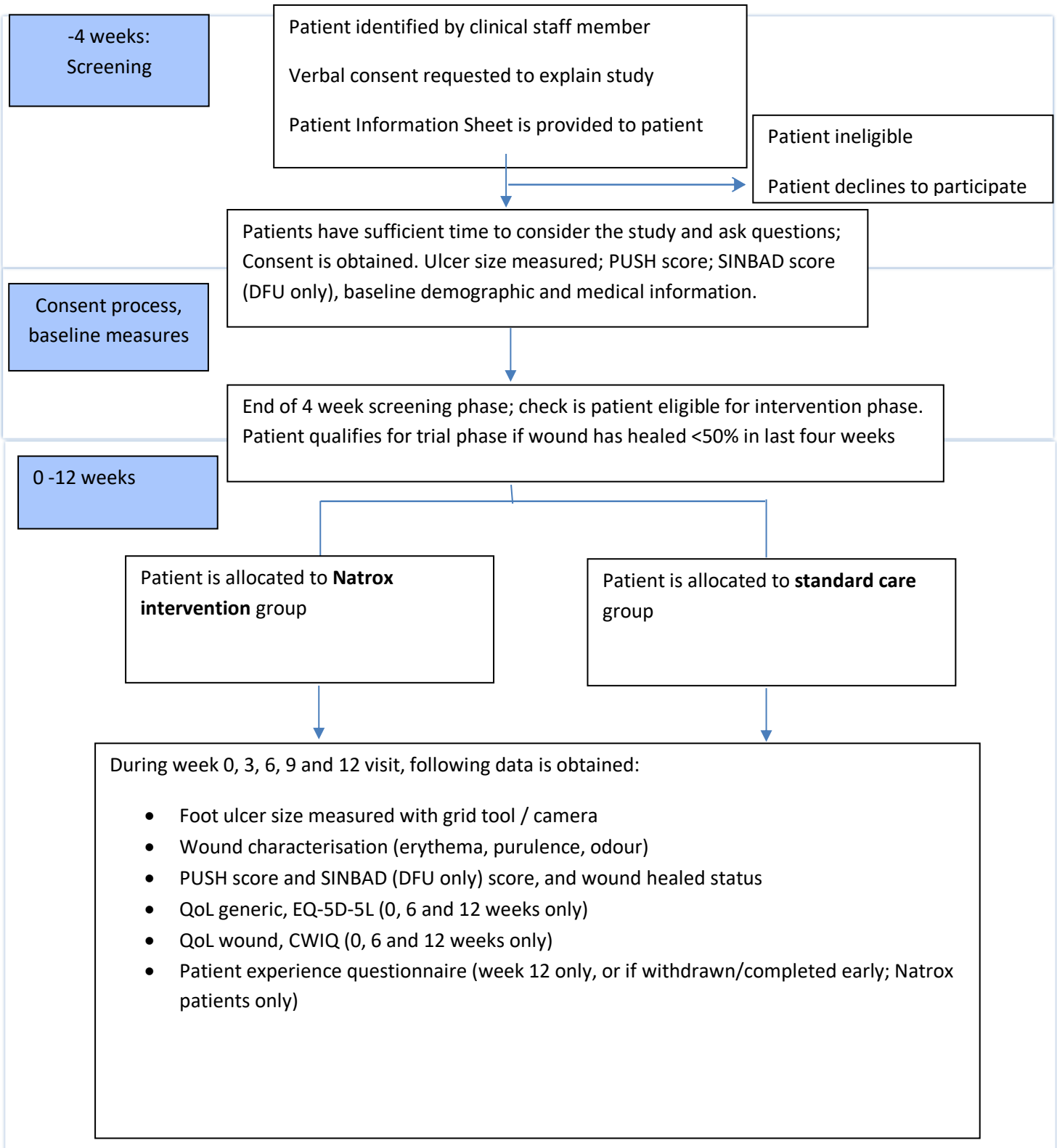
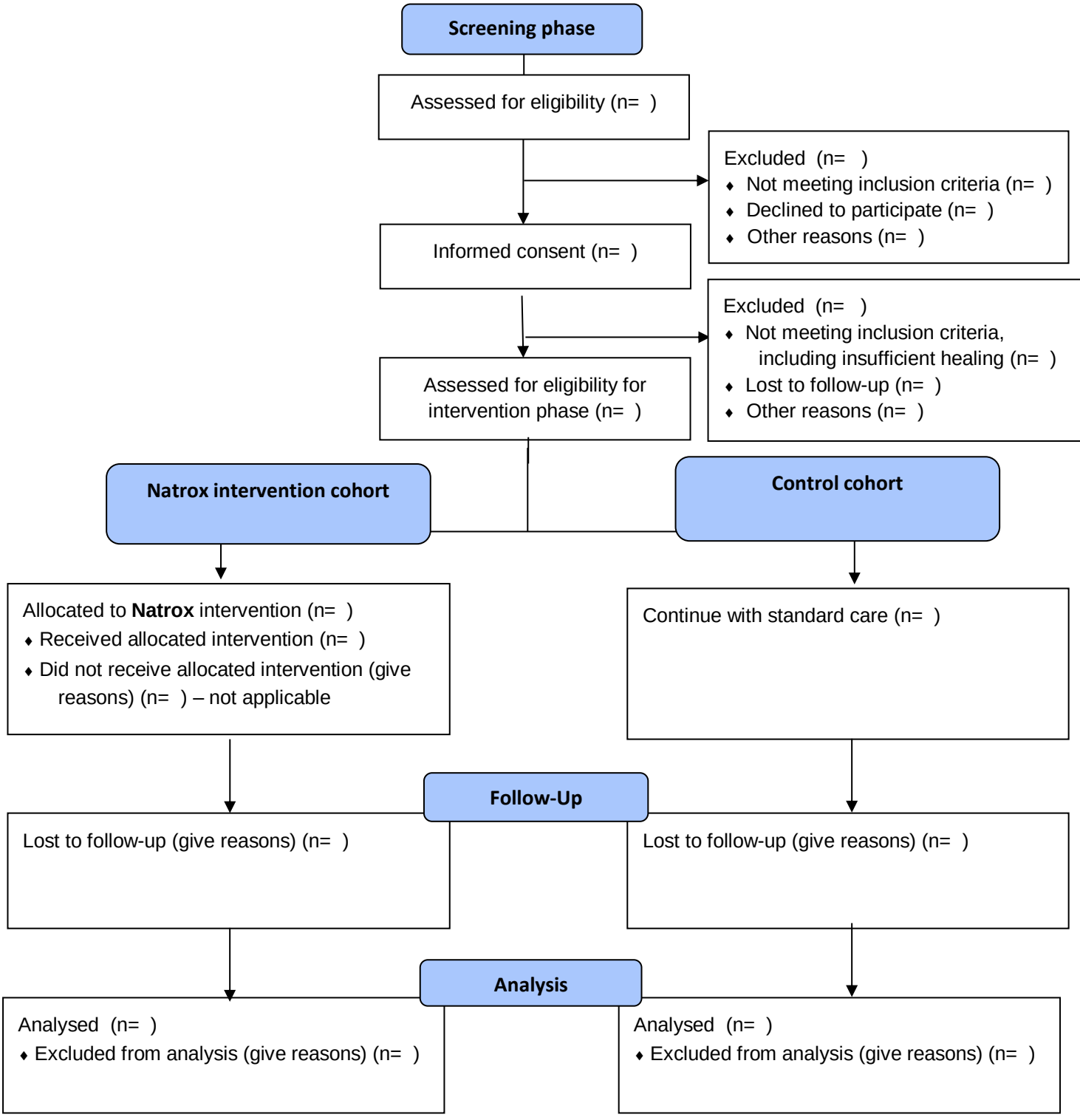
APPENDIX 1. STUDY PARTICIPANT FLOWCHART



APPENDIX 2. CONSORT FLOWCHART



**Based on CONSORT Flowchart*