A model for diabetic foot ulcer clinical trials on advanced therapies

Abstract: Randomised controlled clinical trials remain the gold standard in assessing the efficacy of a medical drug, device or intervention. Standardisation in clinical trial design reduces bias, ensures the validity of the trial data, and allows for generalisation of trial results to the larger real-world population which has the disease. Critics of diabetic foot ulcer (DFU) trials point to the inconsistency in endpoints between studies, a lack of translation to the DFU population at large, failure to include the target population in advanced therapies, and a poorly defined standard of care (SoC). These issues of design and conduct were addressed by the Natrox Topical Oxygen Wound Treatment (NOWT) trial. In the past, DFU clinical trials prescribed dressings that were not SoC, such as wet-to-dry gauze, loosely controlled offloading and debridement. The trials failed to concentrate on DFUs that qualified for advanced wound care from a clinical and payer perspective. A four-week run in period to the NOWT trial matched the requirement for 30 days of SoC before instituting advanced therapy. Sharp excisional debridement was mandated and confirmed through digital photography. Total contact casting was used to offload plantar DFUs. This manuscript uses the NOWT trial as a guide for future DFU clinical trial design.
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More than 25 million people in the US have diabetes and >80,000 patients undergo lower extremity amputation each year due to a diabetic foot ulcer (DFU).[1,2] The mortality rate following amputation surpasses that of most common cancers.[3] Beyond the negative impact on patients' quality of life, the financial cost to the healthcare system exceeds $10 billion USD, annually.[4] Despite the introduction of products designed to promote healing, only 30% of DFUs heal completely by 12 weeks.[5] These sobering statistics highlight the need for advanced therapies to treat DFUs.

The search for advanced therapies that accelerate healing, reduce complications and prevent recurrence remains the focus of the wound healing research community. The primary mechanism for generating evidence for the efficacy of a medical drug, device or intervention is the randomised controlled clinical trial (RCT). Standardisation in clinical trial design reduces bias, ensures the validity of the trial data, and allows for generalisation of trial results to the wider real-world population with the disease. RCTs can also guide payers in making coverage and reimbursement decisions.

Critics of DFU trials point to the inconsistency in endpoints between studies, the use of exclusion criteria that select patients who do not reflect the general wound care population, failure to enrol patients who would qualify for advanced therapies in the real world, and poorly defined or non-prescriptive standard of care (SoC).[6]

The evolution of RCTs in DFUs began in the late 20th century.[7] The SoC consisted of wet-to-dry dressings applied once or twice daily.[8] Debridement was not included in the trial design until the post hoc analysis by Steed et al.,[9] published in 1996, which demonstrated that DFUs in the treatment arm (platelet-derived growth factor) that underwent debridement were more likely to heal in 12 weeks.[9] In early trials, offloading was not well controlled and the incorporation of a run-in period to eliminate rapid healers was not part of the design.[7,8] Unfortunately, standardisation of DFU clinical trial design has progressed slowly. The formation of the Wound Care Collaborative Group, sponsored by the US Food and Drug Administration, has refocused attention on DFU clinical trial design.[10]

The Natrox Oxygen Wound Treatment (NOWT) RCT endeavoured to address the shortcomings in DFU clinical trial design.[11] It had weaknesses, such as a lack of blinding; however, the study successfully managed the deficiencies of past DFU trials. Blinding will continue to be explored in future DFU trials. The trial featured a four-week run in period to eliminate patients with DFUs that displayed a healing trajectory with SoC treatments, and who did therefore not require advanced therapy. Debridement was prescribed and closely monitored. Moisture-balancing dressings were provided to the participating site for use in the trial. Plantar DFUs were offloaded, starting in the run-in period, using total contact casting (TCC). NOWT serves as a model for DFU RCTs. This manuscript uses the NOWT trial as a guide

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for future DFU clinical trial design. A description of the trial is detailed in the Methods section, below.

Methods

NOWT, a multicentre randomised, open label, clinical trial, compared the efficacy of topical oxygen delivered by continuous diffusion (TOT) plus SoC with SoC alone in the treatment of hard-to-heal DFUs. The inclusion and exclusion criteria are shown in Table 1.

Ethical approval and patient consent

The study was performed in accordance with US and international standards of Good Clinical Practice, the Declaration of Helsinki, and was approved by appropriate ethics committees (Western Institutional Review Board (WIRB) No: 20191085) and registered at Clinicaltrials.gov (NCT03905863). All patients provided written informed consent and were reimbursed $100 USD per visit for transportation costs.

Intervention

SoC consisted of wound cleansing with normal saline. Sharp excisional debridement on the initial screening visit was followed by selective or excisional debridement on subsequent visits at the investigator's discretion. The study staff applied a moisture-balancing dressing, depending on the amount of wound exudate. A foam was used for low exudating DFUs and an alginate for moderate-to-heavy exudating DFUs. Patients with active cellulitis were excluded. Once the investigator determined that the foot had adequate perfusion, determined by using ankle-brachial index, toe-brachial index or transcutaneous oxygen measurement, the patient was placed in a TCC. The TCC was changed within 3–4 days following the initial application and then applied weekly on patients enrolled in the trial.

The screening phase entailed the collection of two weeks' of DFU healing data (historical run-in portion). Patients who achieved a percentage area reduction (PAR) of >20% in two weeks were excluded. Patients who did not achieve a PAR of 20% over the previous two weeks were consented and entered the onsite screening phase. Patients who did not have two weeks of PAR data were consented and entered the screening phase for a total of four weeks, assuming there were no other factors that excluded the patient. During phase 2 of screening, all patients received SoC as described above, including sharp excisional debridement and application of a TCC.

After the two-week onsite screening period, patients who met all of the inclusion and none of the exclusion criteria were randomised to receive TOT plus SoC or SoC alone. Exclusion criteria included the failure of the target DFU to heal by >20% during the two-week onsite screening or by 40% over the entire four-week screening run-in.

During the active phase, the trial patients were assessed weekly for 12 weeks. Patients were recruited from June 2019 to June 2020. Patients randomised to the treatment arm received TOT (Natrox Generator and Natrox Oxygen Delivery System (Inotec AMD Ltd., UK, Fig 1) in addition to SoC.

Fig 1. Continuous topical oxygen therapy device (Natrox Oxygen Wound Therapy, Inotec AMD Ltd., UK

The device's generator uses water electrolysis, and the delivery system delivers 11ml/hour of oxygen continuously to the wound site. The batteries last 24 hours. Patients were given two rechargeable batteries: one to run the system and the second to be charging.

Results

A total of 19 centres across the US screened 224 patients and enrolled 145 patients. The goal was to evaluate topical oxygen therapy in Medicare beneficiaries. The results were published in the *Journal of Wound Care* in 2021.[11]

For the purpose of this study, several aspects of the results are highlighted. The two groups had similar demographics (Table 2). The CONSORT diagram (Fig 2), shows that 79 patients were excluded at the screening stage. The most common reason was healing >20% during the two-week onsite screening period (43%). Most of these patients had DFUs for >3 months. SoC including sharp debridement resulted in rapid healing and obviated the need for advanced therapy. In addition, more than half of the patients were ≥65 years of age.

Discussion

The adoption of a four-week run-in period to eliminate 'rapid healers' permitted the selection of patients with hard-to-heal wounds most likely to benefit from the intervention. This technique homogenised the study population and excluded patients who would heal independent of the treatment received. From a practical point of view, the trial design ensured that the population receiving the active treatment best mirrored the real-world patients who would benefit from the intervention. In other words, RCTs that select rapid healers or relatively easy-to-heal subjects

Table 1. Inclusion and exclusion criteria for the Natrox Topical Oxygen Wound Treatment diabetic foot ulcer trial[11]

Inclusion criteria	Exclusion criteria
Subjects are male or female, ≥18 years of age. At least 50% of the enrolled population must be ≥65 years of age	Subject has a known life expectancy of <1 year
Subjects with one of the following wounds: • Diabetic foot ulcer present for >4 weeks (documented in the medical record) but <12 months' duration if being treated with active standard of care (SoC) • Minor amputation wound sites	Subject or caregiver is unable to manage the Natrox device (charge and change batteries daily)
Subject has clinical documentation of no visible wound improvement after four weeks of SoC. Objectively, <40% healing in the past four weeks from the first treatment visit	Subject has ulcers that are completely necrotic or if the clinician feels it is clinically necessary to cover the wound surface in gel or creams that would prevent the transmission of oxygen to the wound surface
Study ulcer is a minimum of 0.5cm^2 and a maximum of 25cm^2 at first treatment visit (if a patient had >1 active ulcer that fitted the inclusion criteria, then the largest ulcer was identified as the 'index' ulcer)	Subject has major uncontrolled medical disorders, such as serious cardiovascular, renal, liver or pulmonary disese, lupus, palliative care or sickle cell anaemia
Subject's wound score on the Infectious Disease Society of America's tool is Grade 1 or 2	Subject currently being treated for an active malignant disease or subjects with a history of malignancy within the wound
Subject is able and willing to follow the protocol requirements	Subject has other concurrent conditions that, in the opinion of the investigator, may compromise subject safety
Subject has signed informed consent	Known contraindications for the Natrox system
Adequate circulation to the affected foot as demonstrated by a dorsum transcutaneous oxygen measurement or a skin perfusion pressure measurement of ≥30mmHg; an ankle-brachial index between 0.7–≤1.3, or toe-brachial index of >6 within three months of first screening visit	Known allergies to any of the Natrox system components
Females of childbearing potential must be willing to use acceptable methods of contraception (birth control pills, barriers or abstinence)	Concurrent participation in another clinical trial that involves an investigational drug or device that would interfere with this study
Index ulcer has been offloaded with a total contact cast (unless an exemption was requested, in which case a fixed ankle walker) for at least 14 days prior to randomisation	Index ulcer has reduced in area by ≥20% after two weeks of SoC from the first screening visit to the treatment visit 1/randomisation visit
	Subject is pregnant or breastfeeding
	Subjects with a history of >2 weeks' treatment with immunosuppressants (including systemic corticosteroids >10mg daily dose), cytotoxic chemotherapy or application of topical steroids to the ulcer surface within one month prior to first screening visit, or who receive such medications during screening period, or who are anticipated to require such medications during the course of the study
	Index ulcer has been previously treated with tissue-engineered materials or other scaffold materials (cellular, acellular, matrix-like products) within the 30 days preceding the first treatment visit
	Affected extremity requiring hyperbaric oxygen during the trial or within two weeks of treatment visit 1
	Known haemoglobin A1c >12%
	An ulcer that has visible signs of improvement in the four weeks prior to randomisation, defined objectiely as a 40% reduction in surface area in the four weeks prior to enrolment
	An ulcer that has healed by >20% in the two weeks prior to screening: 'historical' run-in period

may demonstrate the efficacy of an intervention but may not have any practical application in the wound clinic population. The four-week run-in period reflects Medicare's requirement of 30 days of basic wound care prior to using advanced wound therapies. The enrolment of patients aged ≥65 years also ensured that the treatment was applicable to the Medicare population.

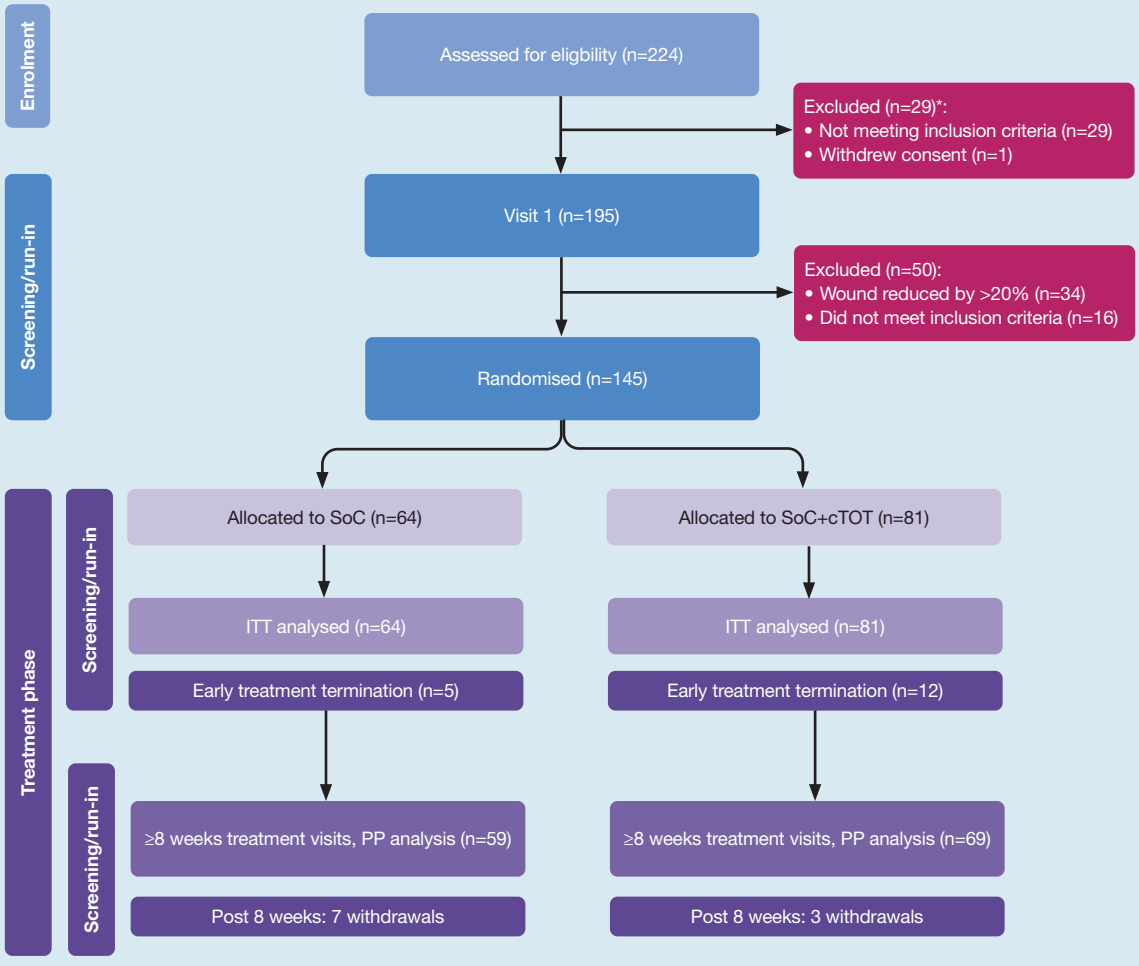
The NOWT protocol clearly prescribed a stringent SoC. Sharp excisional debridement was mandated and monitored. The lead investigator and clinical research associates monitored pre- and post-debridement wound photographs uploaded into the electronic data capture system (Tissue Analytics, Net Health, US) at least weekly. Excisional debridement was required on the initial screening visit after adequate perfusion was confirmed.

Table 2. Patient demographics for the Natrox Topical Oxygen Wound Treatment diabetic foot ulcer trial[11]

Baseline characteristic	SoC (n=64)	SoC+cTOT (n=81)
Age at inclusion, years, mean±SD Minimum, maximum	62.69±12.56 34, 91	64.20±14.15 33, 93
Sex, n		
Female	11	26
Male	53	54
Not declared	0	1
Currently using tobacco, n		
Yes	11	11
No	51	68
Not declared	2	2
Diabetes duration, years*, mean±SD Minimum, maximum	18.33±11.35 3, 62	18.35±13.53 1, 55
Body mass index, kg/m^2†, mean±SD Minimum, maximum	31.00±7.79 19, 51	30.80±6.83 16, 54

*SoC n=60; SoC+cTOT, n=76; †Missing data of five patients in each group; cTOT—continuous topical oxygen therapy; SD—standard deviation; SoC—standard of care

Fig 2. CONSORT diagram for the Natrox Topical Oxygen Wound Treatment diabetic foot ulcer trial.[11] cTOT—continuous topical oxygen therapy; ITT—intention to treat; PP—per protocol; SoC—standard of care. *One patient counted twice, hence total of 29 excluded



Wet-to-dry dressings are no longer an acceptable DFU dressing in clinical trials. The dressing must maintain an appropriate moisture balance, avoiding maceration of the surrounding skin while preventing desiccation of the tissues.[12] The NOWT trial allowed the investigators to use an alginate dressing for DFUs with moderate-to-high exudate and a foam dressing for low exudating DFUs. There were no adverse events related to inappropriate moisture balance. In conducting clinical trials, it is essential to supply the dressings to the research centres to ensure uniformity in both study arms, thereby reducing intervention bias. The dressings were marked as investigational and used only on patients participating in the trial.

TCC is the SoC for offloading the diabetic foot. Studies have demonstrated its superiority over other forms of offloading.[13,14] Sponsors and investigators have hesitated to use TCC in clinical trials for a variety of reasons: unfamiliarity with the procedure; patient acceptance; the time required to place a TCC; cost; and the need for frequent dressing changes. Despite these obstacles, TCC represents the most effective method for ensuring adequate offloading in all arms of the study. In the NOWT trial, TCC was mandated for all plantar DFUs on every visit. This ensured that both treatment and SoC arms received sufficient offloading. The application of TCC began in the screening phase. This may explain the high screening failure rate due to rapid healing. It also suggests that the patients had not received appropriate offloading, which is SoC for DFU management, prior to screening. Using TCC during the run-in phase and continuing throughout the trial ensured that each patient received appropriate offloading prior to enrolment, eliminating rapid healers who did not require advanced therapy, and improving the reliability of the data. DFU clinical design should include TCC or an equally effective offloading procedure, beginning in the screening phase and extending throughout the trial.

Limitation

A limitation of the NOWT trial was the lack of blinding. Double-blinding in clinical trials reduces bias.[15] At the time of the NOWT trial, the technology to blind the trial was not available; however, ongoing clinical trials incorporate blinding into their protocol. Blinding is difficult in wound healing trials. Devices often do not have an acceptable sham treatment. Trials evaluating the efficacy of cellular and or tissue-based products for wound care, for example, do not have an inert version similar in appearance. Trial design may include a blinded evaluator to achieve single-blinding; however, this increases the complexity and cost of the trial.

Conclusion

The NOWT DFU clinical trial serves as a model for future clinical trials in DFUs designed for regulatory approval and reimbursement. **JWC**

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Reflective questions

- Would standardisation of clinical trials in diabetic foot ulcers (DFUs) improve interpretation of clinical efficacy and facilitate product reimbursement?
- What is the best design for a DFU clinical trial?
- What is the efficacy of topical oxygen in DFUs?