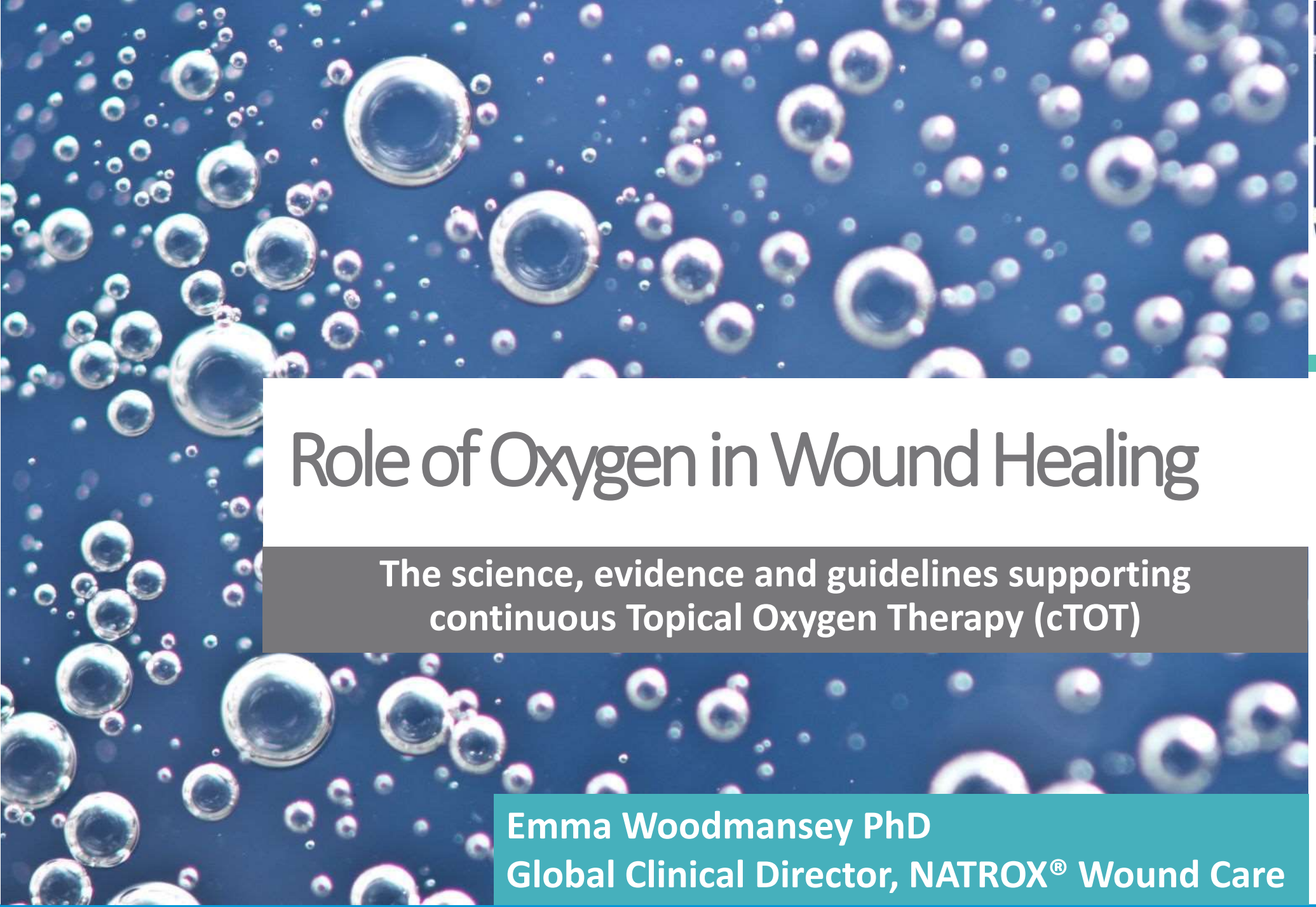


WHASA
Wound Healing Association of Southern Africa

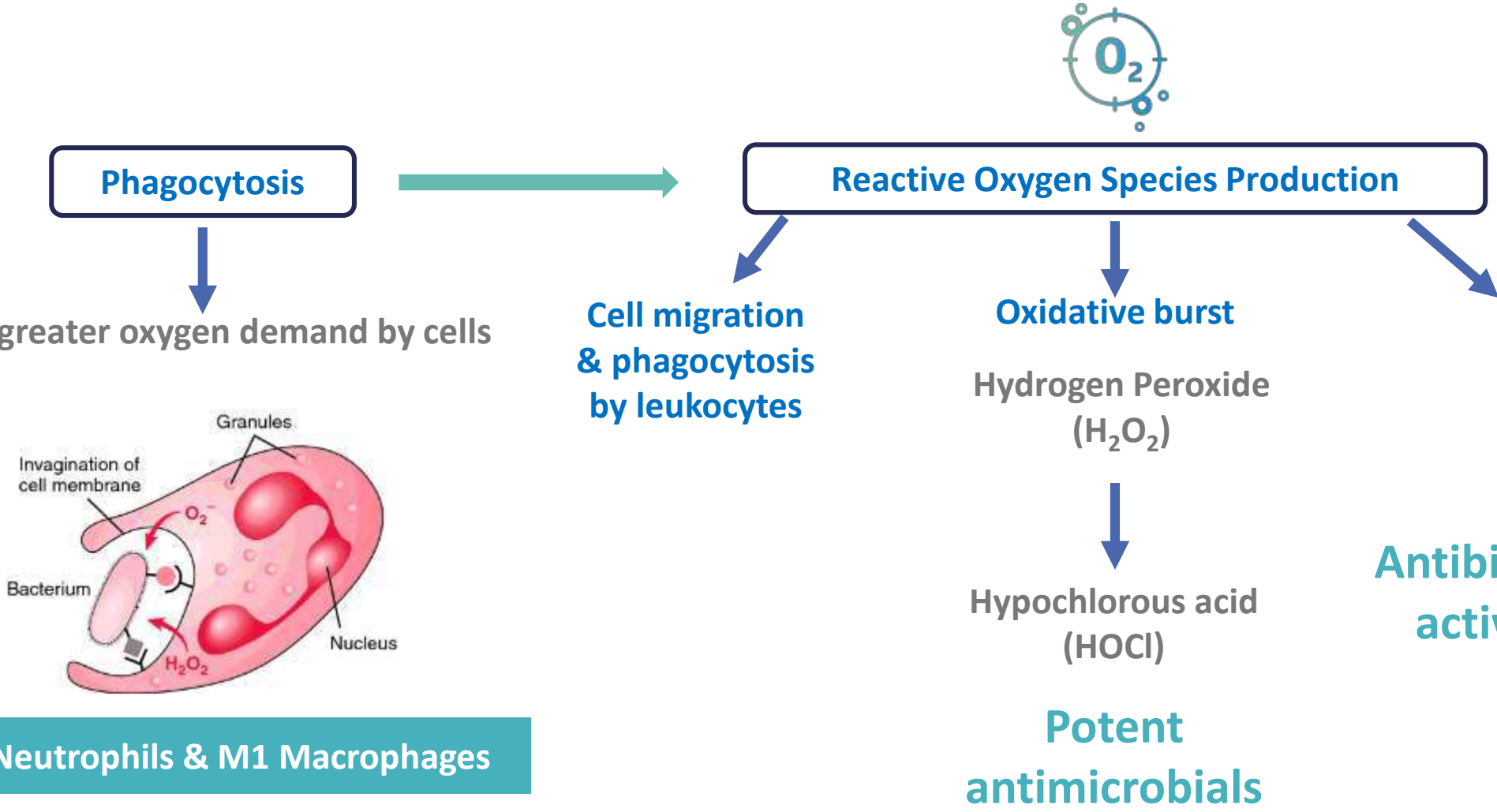
Role of Oxygen in Wound Healing

The science, evidence and guidelines supporting continuous Topical Oxygen Therapy (cTOT)

Emma Woodmansey PhD
Global Clinical Director, NATROX® Wound Care

NATROX® O_2

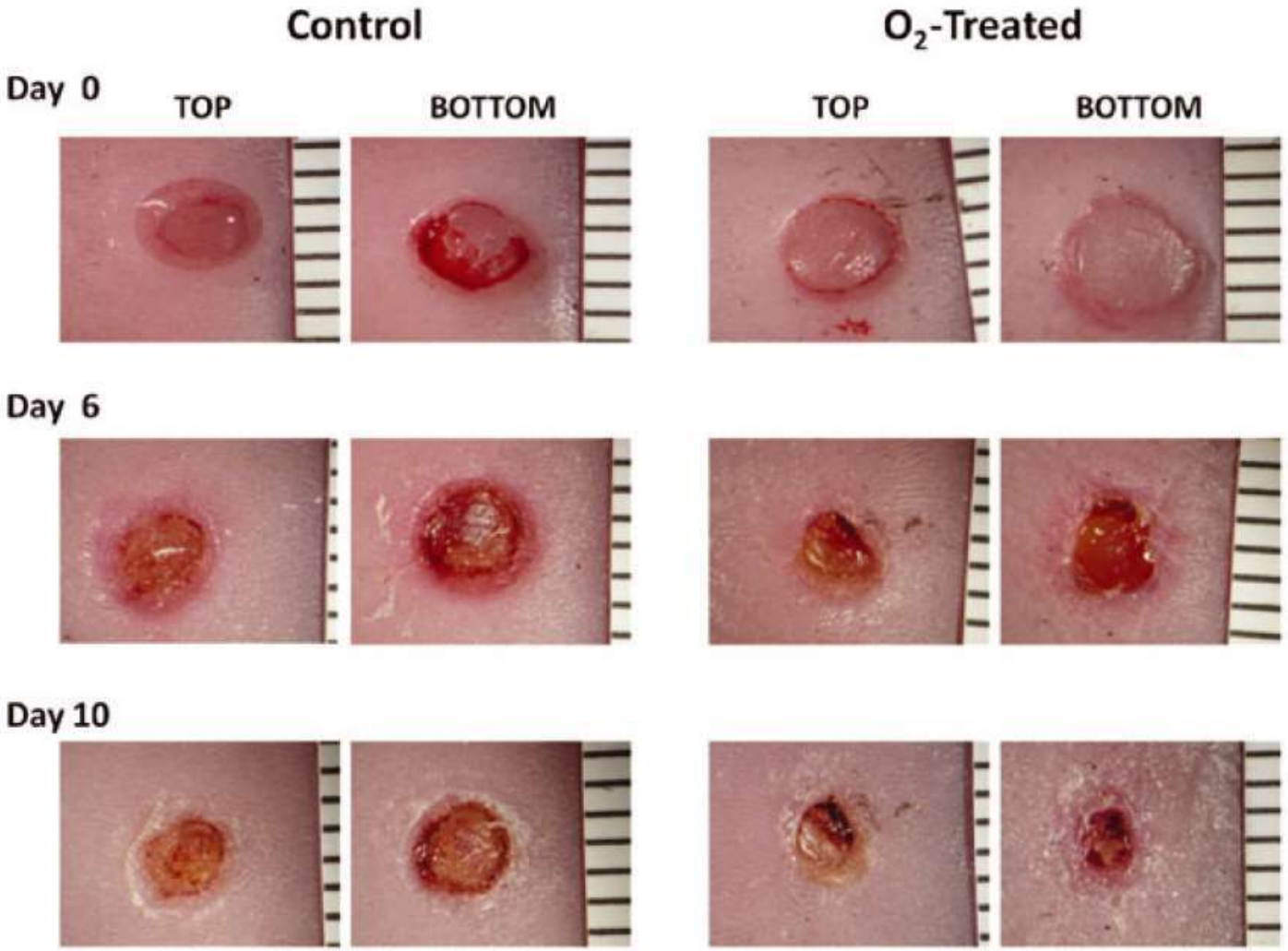
Critical Role of Oxygen Against Infection



Frykberg, R. *et al.* Use of Topical Oxygen Therapy in hard to heal wounds. *J Wound Care* 32, S1–S32 (2023).

TOT Increases Epithelialization in Diabetic Skin Wound Model

Mouse model of diabetic skin wounds: TOT vs Control



EPITHELIALIZATION

Mean reduction of wound size

- Day 6: 60% (TOT) vs. 45% (Control)
- Day 10: 83% (TOT) vs. 71% (Control)

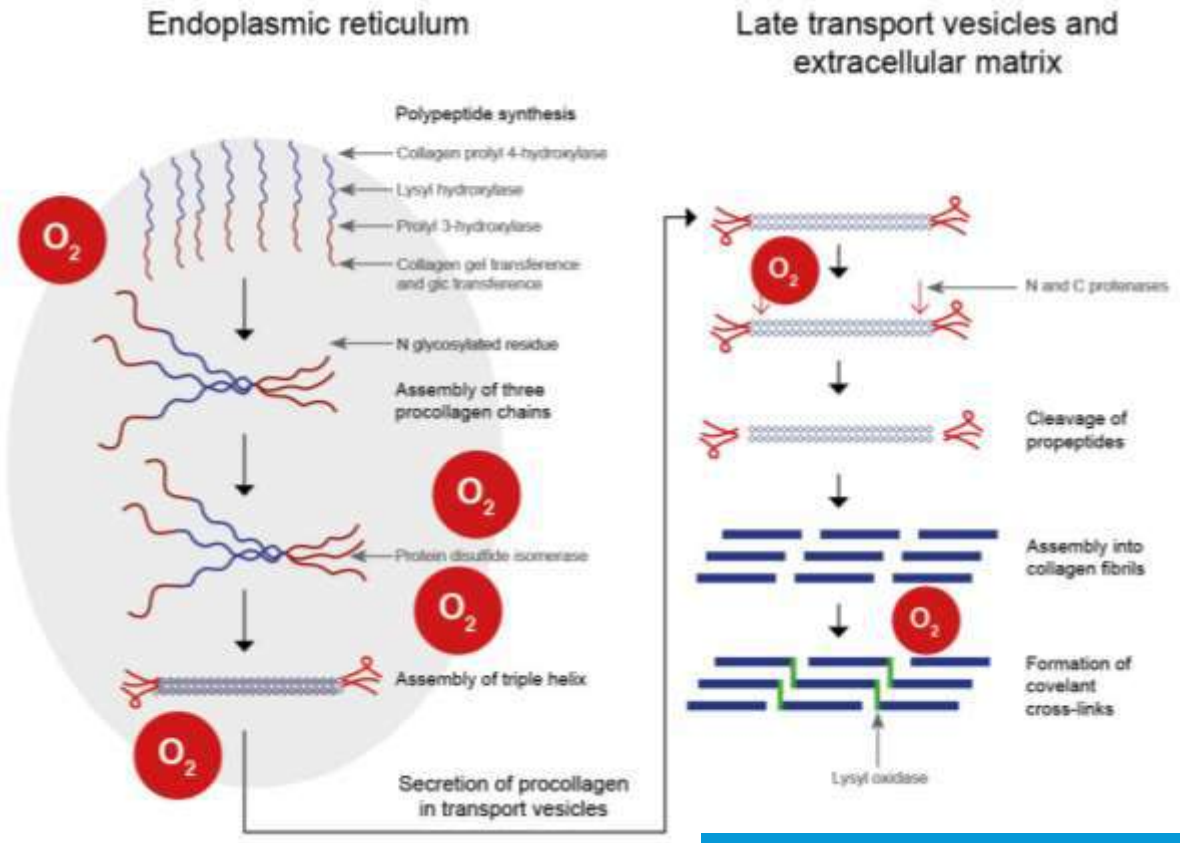
Complete re-epithelialization at Day 10 in **57% TOT wounds** vs. **25 % control**

COLLAGEN RE-MODELLING

- Increased collagen deposit at wound base after TOT.
- Collagen fibres appear more organised, fibrous appearance with TOT
- Suggests remodelling significantly more advanced than in control.

Asmis, R., Qiao, M. & Zhao, Q. Low flow oxygenation of full-excisional skin wounds on diabetic mice improves wound healing by accelerating wound closure and reepithelialization. *Int Wound J* 7, 349–57 (2010).

Remodelling: Collagen Synthesis & Stability O_2 Dependent



Collagen deposition, polymerization (enzymes prolyl hydroxylase & lysyl hydroxylase) and covalent cross-linking require optimal levels of molecular oxygen

Low O_2 - collagen hydroxylation and maturation ***reduced*** and ***collagen remains fragile;*** new vessels fail to mature and break.

Collagen deposition proceeds in direct proportion to *p*O_2

- new vessels cannot even approach their greatest possible rate of growth unless the wound tissue *p*O_2 is high

Collagen formed in hypoxic environments **only 30% as strong** as collagen formed in normal oxygen concentrations.

Sen, C. K. Wound healing essentials: Let there be oxygen. *Wound Repair and Regeneration* **17**, 1–18 (2009).

Reasons for Wound Hypoxia

HYPOXIA = Reduction in oxygen delivery below tissue demand

Patient

- Peripheral Vascular Disease (PVD)
- Oedema
- Damage to blood vessels due to comorbidities (e.g. diabetes)
- Co-incident conditions (e.g. infection, pain, anxiety and hyperthermia)
- Compromised pulmonary health (e.g. COPD)

Wound

- Micro-vasculature/ capillary damage due to trauma
- Contraction of vessels in traumatized tissue
- Oedema
- Necrotic tissue
- Infection / Biofilm – further tissue damage

Cellular activity

- Infection: Bacterial & fungal proliferation consume energy
- Host cells need energy (ATP) to function
- Immune cells (migration, phagocytosis, de-granulation, differentiation)
- Immune response – Production of Reactive Oxygen Species
- Migration & repair (epithelial cells)

Sen, C. K. Wound healing essentials: Let there be oxygen. *Wound Repair and Regeneration* **17**, 1–18 (2009).

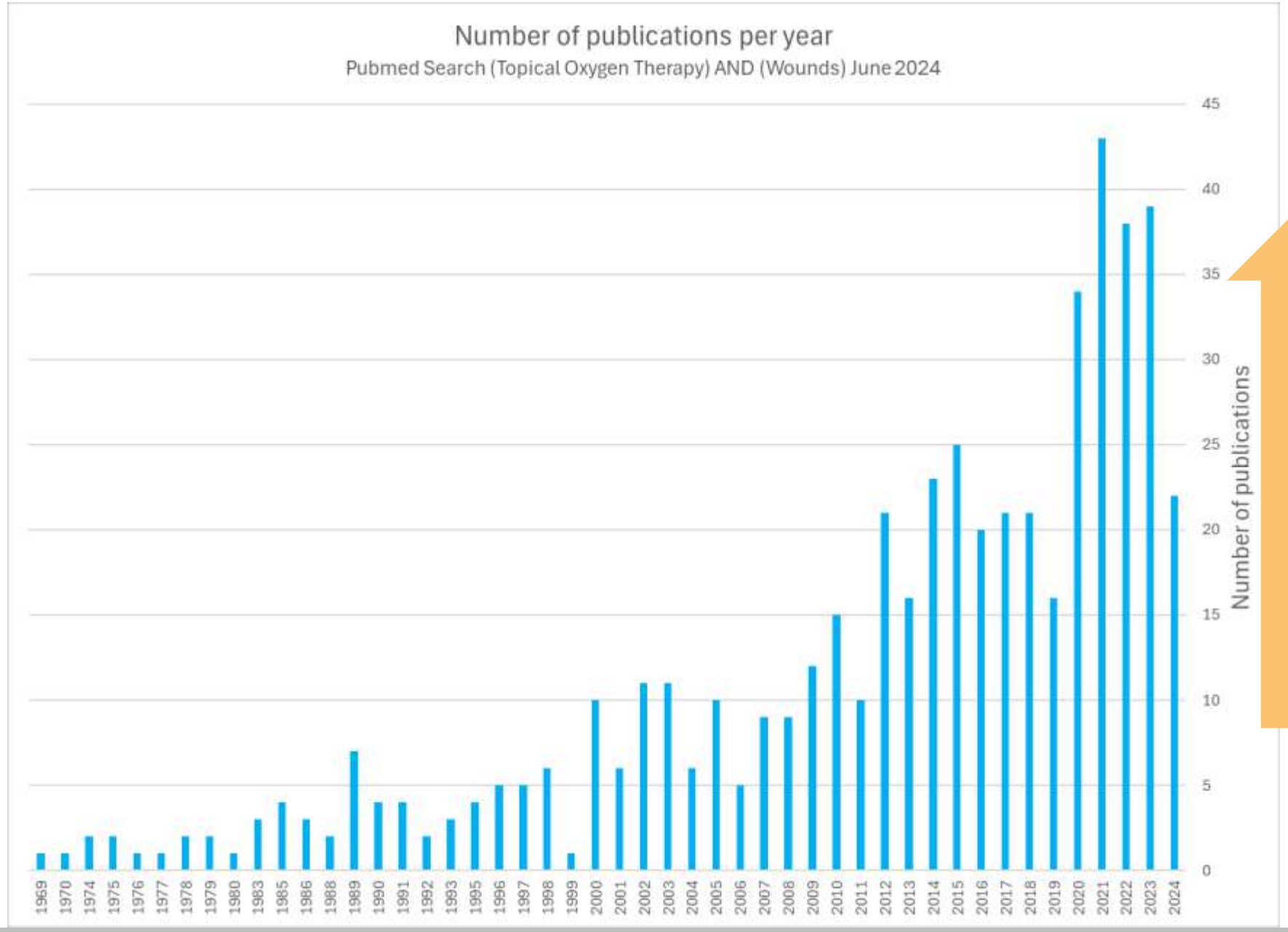
NATROX® O_2 - Simple Technology in Action

1. Oxygen Generator (OG)

2. Batteries (rechargeable)

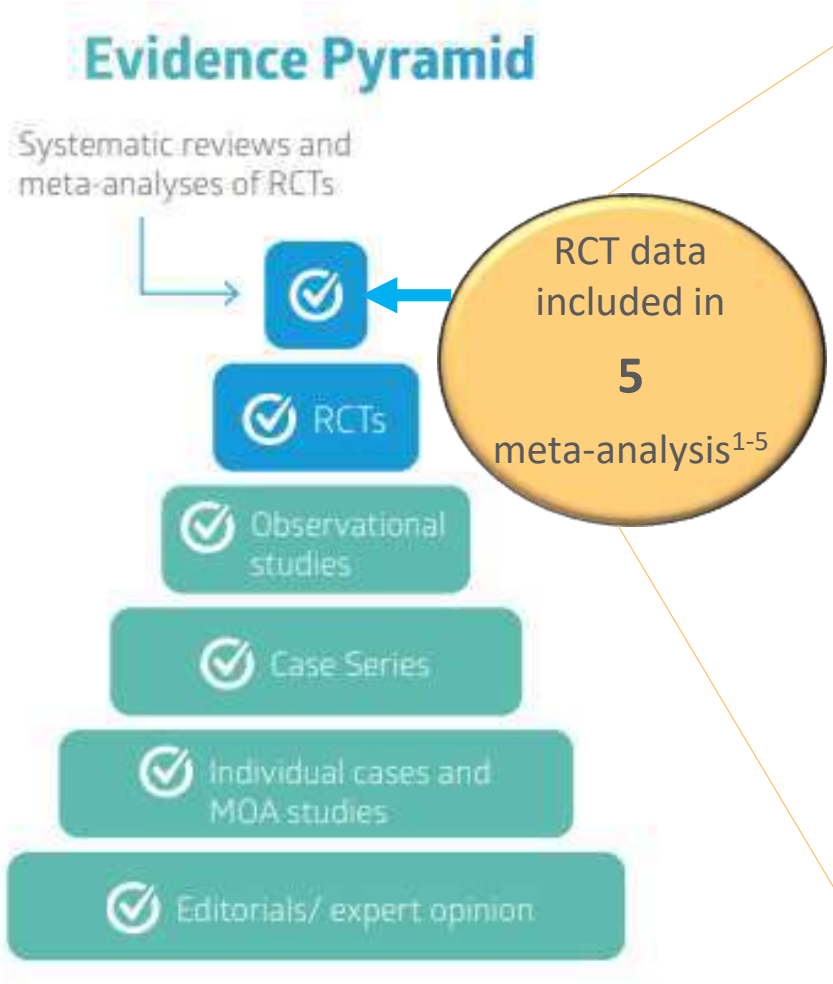
3. Oxygen Delivery System (ODS)

Practical for carer and patient



Evidence is GROWING for TOPICAL OXYGEN THERAPY

cTOT High Evidence Levels



	Author	Study	Wound	Intervention	Key Outcomes
SLR & Meta-analysis	Carter 2023[1]	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	**A random-effects meta-analysis of four RCTs showed that TOT improved wound healing at 12 weeks over SOC alone - supporting the use of TOT for the treatment of chronic Wagner 1 or 2 DFU in the absence of infection and ischemia** The overall GRADE level of evidence for TOT was moderate RR: 1.59; 95% CI: 1.07–2.37; p = 0.021
	Sethi 2022[2]	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	**Meta-analysis of four RCT's demonstrated that use of adjuvant TOT showed higher rate of complete by approximately 60% at 12 weeks wound healing in DFU compared to SoC alone** RR: 1.59; 95% CI: 1.07–2.37;p = 0.021. RR 1.59 95% confidence interval 1.07, 2.37 p = 0.02; NNT 6.3
	Sun 2022[3]	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	**Meta-analysis of seven trials demonstrated that TOT group had higher healing rate with no effect on adverse events** RR = 1.63, 95% CI [1.33, 2.00] p=0.096
	Thanigaimani 2021[4]	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	**Meta-analysis of six RCT's showed TOT significantly increased the likelihood of ulcer healing compared to controls** RR 1.94; 95% CI 1.19, 3.17; I2 = 57%; NNT = 5.33 p=0.04
	Connaghan 2021[5]	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	**Meta-analysis of five RCT's demonstrated that DFUs are >2 times more likely to heal with TOT than with SoC alone.** OR healing 2.49 (95% CI: 1.59– 3.90; p=0.00001 Z=4.00 (p<0.0001)

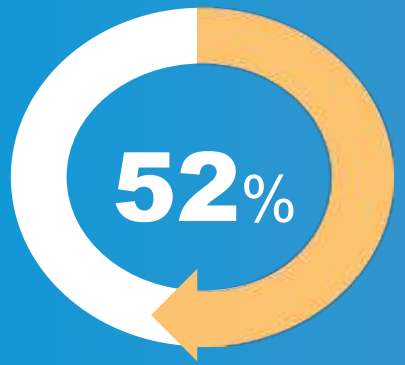
1. Carter, M. J. *et al. Adv Wound Care (New Rochelle)* **12**, 177–186 (2023), 2. Sethi, A., *et al. Health Sciences Review* **3**, 100028 (2022), 3. Sun, X. *et al. Int Wound J* **19**, 2200–2209 (2022), 4. Thanigaimani, S.,*et al. Diabetic Medicine* **38**, (2021), 5. Connaghan, F., Avsar, P., Patton, D., O'Connor, T. & Moore, ZJ Wound Care 30, 823–829 (2021)

cTOT RCT

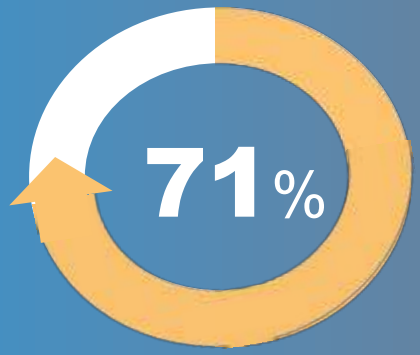

research

Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial

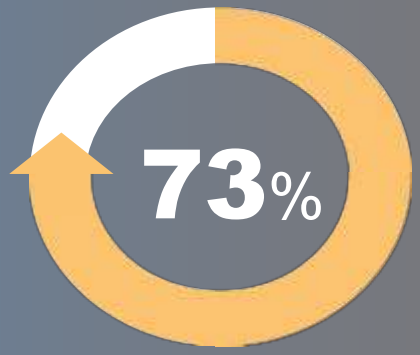
Results for the NATROX® Per Protocol* Group



Healed completely



Greater healing rate**



Greater average % reduction in wound size**

** Compared to control

*145 patients were recruited onto the trial – this is referred to as “intention to treat” (ITT). Those that completed the trial are referred to as “per protocol” (PP), 128 patient completed the study.

Serena, T. E. *et al.* Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *J Wound Care* **30**, S7–S14 (2021).

cTOT and Durability – RCT follow up

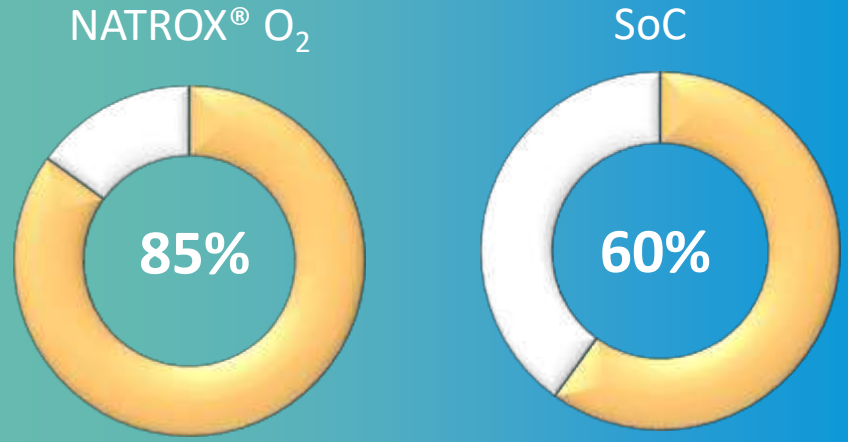
- Follow up study to the RCT
- 22 patients participated

A multicenter clinical trial evaluating the durability of diabetic foot ulcer healing in ulcers treated with topical oxygen and standard of care versus standard of care alone 1 year post healing

Omar Al-Jalodi | Megan Kupcella | Kristy Breisinger | Thomas E. Serena

RESULTS:

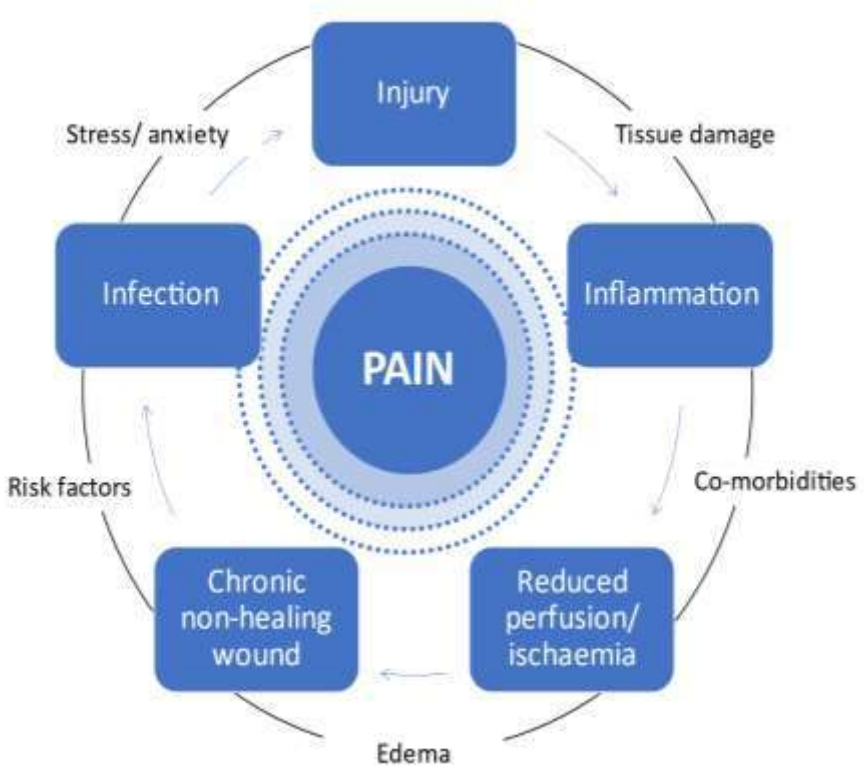
Patients that remained healed at one year

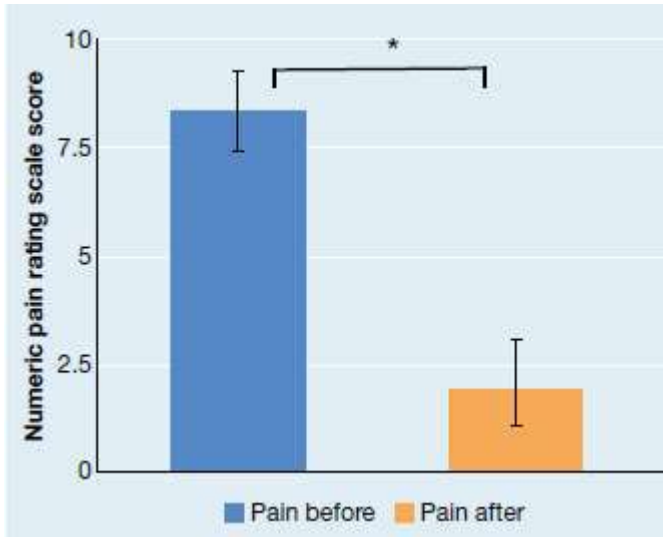


Only 1 major amputation occurred, which was in a SoC-treated patient.

Al-Jalodi, O., Kupcella, M., Breisinger, K., et al. (2022) A multicenter clinical trial evaluating the durability of diabetic foot ulcer healing in ulcers treated with topical oxygen and standard of care versus standard of care alone 1 year post healing. *International Wound Journal*, 19(7) pp. 1-5.

Pain reduction and improved healing VLUs



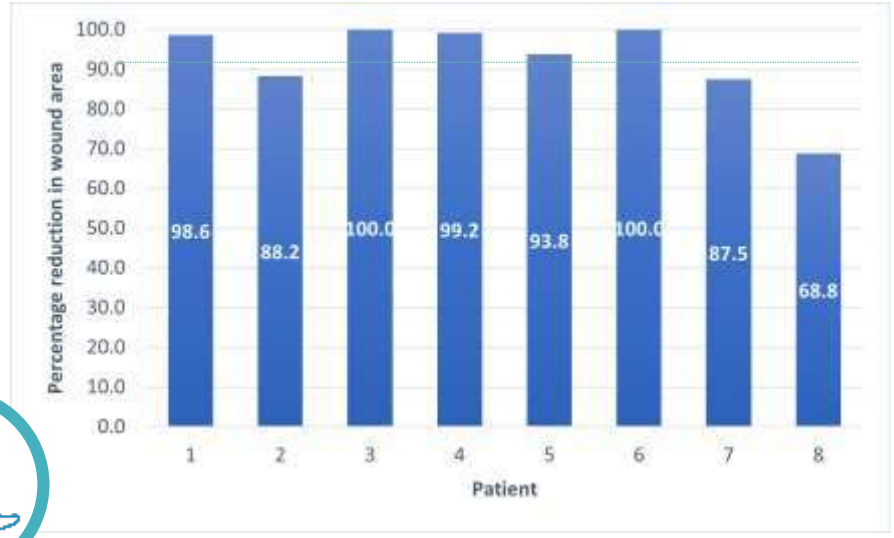


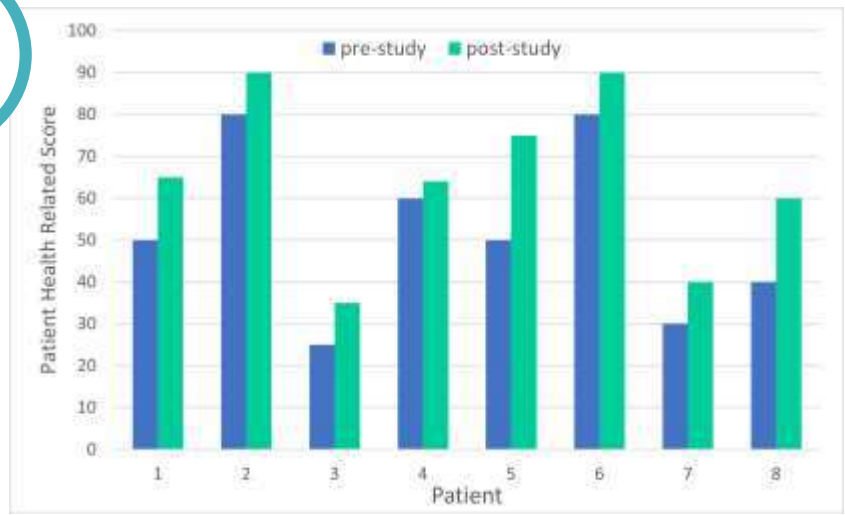
Leg ulcer pain before (mean 8.2) and after (mean 1.9) topical continuous oxygen treatment using the numeric pain rating scale: average patient data *p<0.00001. Error bars indicate standard error

- **40% of hard to heal wounds healed with cTOT**
- **Significant reduction in wound pain after cTOT (p<0.00001)**
- **69% patients stopped taking opioids**

Jebril, W. *et al.* Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series. *J Wound Care* **31**, 4–11 (2022).

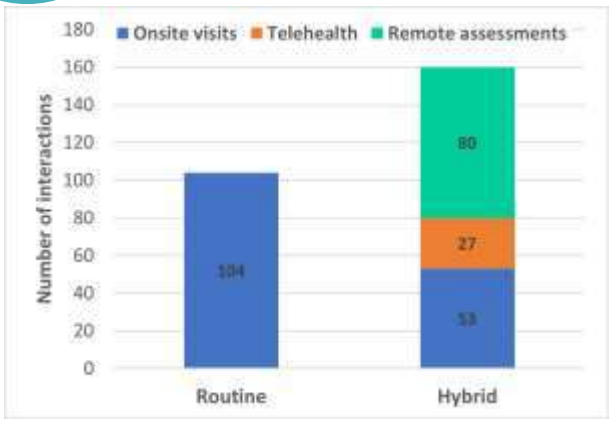
Shared care - outcomes



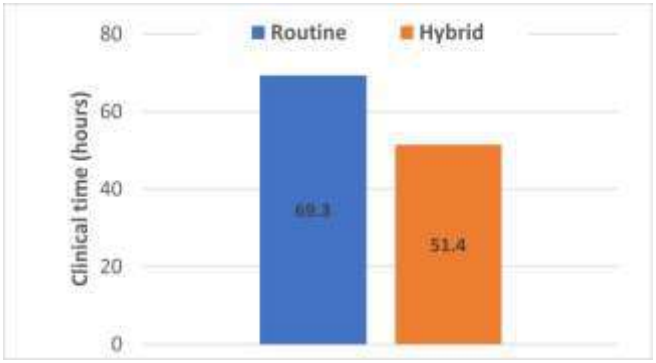


Improved PRHS QoL in all 8 patients

54 % increase clinical interactions

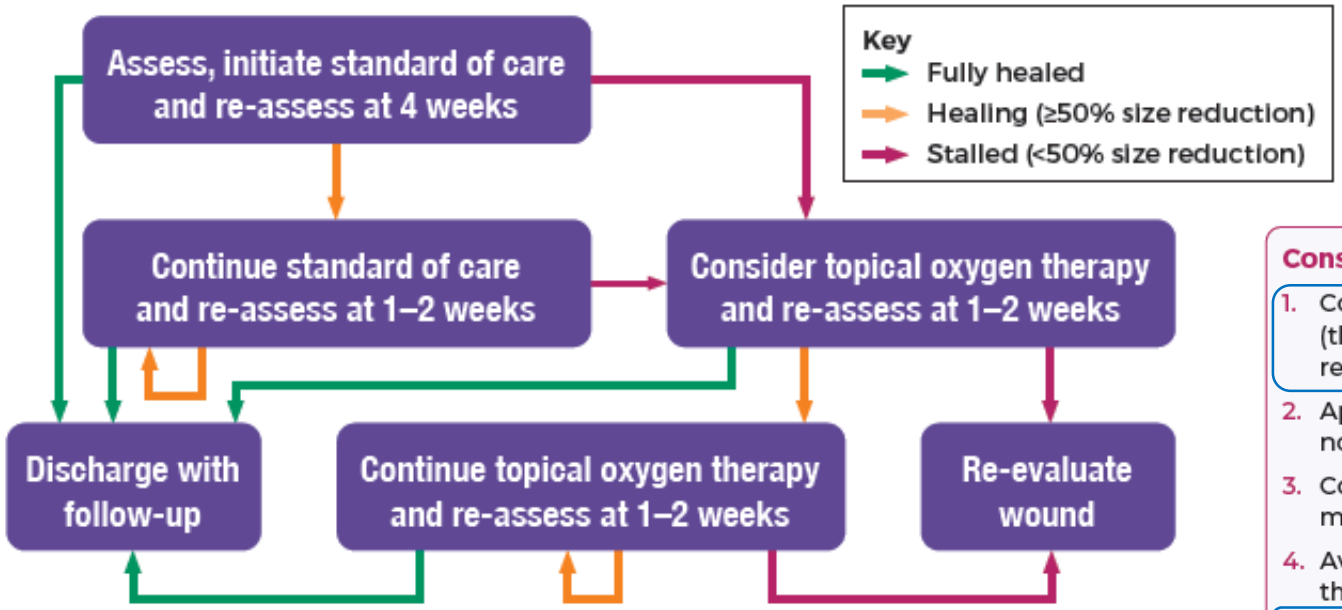


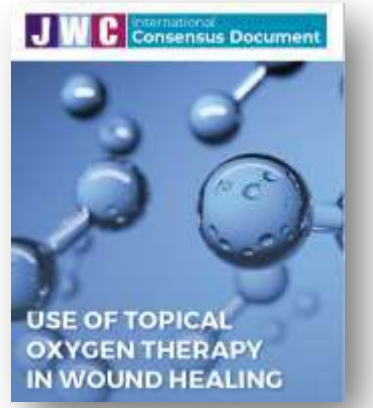
25.8 % reduction in clinical time



Lee, A., Woodmansey, E., Klopfenstein, B., O'Leary, J. L. & Cole, W. Remote assessment and monitoring with advanced wound therapy to optimise clinical outcomes, access and resources. *J Wound Care* **33**, 90–101 (2024).

International Consensus on TOT





Consensus panel recommendations

1. Consideration in hard-to-heal wounds (those that have failed to achieve a 50% size reduction after 4 weeks of standard of care)
2. Applicability to most kinds of non-neoplastic hard-to-heal wounds
3. Contraindication in untreated infection, malignancy or necrosis
4. Avoidance in critical limb ischaemia while there is insufficient evidence
5. Earlier rather than later consideration
6. Initial vascular assessment and possible vascular intervention
7. Frequent and adequate debridement
8. Adjunctive use alongside standard of care
9. Treatment of underlying aetiology, such as offloading, compression or glucose control
10. Management of any pain, infection or comorbidities
11. Avoidance of wound dressings that might impede oxygen diffusion
12. Multidisciplinary approach to treatment
13. Appropriate training to facilitate self-administration by patients or caregivers
14. Broad access, with appropriate reimbursement by payers and healthcare systems
15. Education of providers, insurers and payers on cost-efficacy of treatment
16. Collection of health-economic data on cost-effectiveness in different wound types
17. Creation of a European or global wound register to further evaluate benefits
18. Development of assessment tools to identify regional ischaemia
19. Research into potential as a first-line therapy

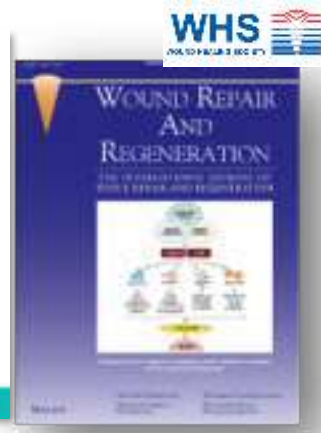
Frykberg, R. *et al.* Use of Topical Oxygen Therapy in Wound Healing. *J Wound Care* **32**, S1–S32 (2023).

International Working Group for the Diabetic Foot 2023

- The evidence on topical oxygen has substantially expanded in the last four years with several new RCTs
- **"Consider the use of topical oxygen as an adjunct therapy to standard of care for wound healing** in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention"

1. Chen, P. *et al.* www.iwgdfguidelines.org (2023)

TOT Recommendations – International Guidelines



1. ElSayed, N. A. *et al.* 12. *Diabetes Care* **46**, S203–S215 (2023)
2. ElSayed, N.A. et al. 12. *Diabetes Care* 47 (Suppl. 1):S231–S243 (2024)
3. Chen, P. *et al.* www.iwgdfguidelines.org (2023)
4. Bem, R. *et al.*. *Journal of Wound Care* **32**, 264–272 (2023)
5. Pacheco YJ, et al. JWC LATAM Supplement Oct 2;32(LatAm sup 10):1-37 (2023)
6. Health Technology Assessment guidance Wales, September 2022
7. Lavery, L. A. et al. WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair and Regeneration (2023)

ADA Standards of Care in Diabetes 2023 & 2024[1,2]

TOT receives an **"A grade" recommendation** as an adjunctive treatment **for chronic DFUs** based its strength of evidence

International Working Group on the Diabetic Foot (IWGDF) 2023[3]

"Consider the use of **topical oxygen** as an adjunct therapy to standard of care for **wound healing** in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention"

A new algorithm for the management of diabetic foot ulcer 2023[4]

Clinical experts in Europe agree that adjunctive treatments with a clear evidence base (cTOT) should be included in the treatment algorithm and "All hard-to-heal wounds are likely to benefit from TOT, even after revascularization"

Expert led Delphi consensus document in South America 2023[5]

"..expert consensus supports the efficacy and safety of continuous transdermal oxygen in the treatment of chronic and/or difficult-to-heal ulcers"

Positive Health Technology Guidance – Wales UK 2022[6]

"cTOT should be adopted in Wales and if not justify why it has not been followed"

WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines 2023[7]

'Level 1 Evidence' recommendation for topical oxygen therapy - "Topical oxygen has been shown to increase the incidence of healing and decrease the time to heal"

Oxygen is essential for multiple critical functions during wound healing

- Many chronic wounds have low oxygen levels which can be supplemented with Topical Oxygen Therapy (TOT).
- TOT use is supported by high level evidence and is recognised in multiple expert guidelines globally.
- NATROX® O_2 cTOT is a simple, easy to use evidence-based technology that can support improved wound healing and allow patients to return to everyday activities.