CPAG Summary Report for Clinical Panel – URN 1779, Hyperbaric Oxygen Therapy for Diabetic Lower Limb Ulceration Refractory to Best Standard Care

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [A]	This is an assessment of the incidence of adverse effects resulting from HBOT. Fedorko et al (2016) was the better study in that reports were made by participants blind to their treatment allocation. Participants reported the incidence of solicited adverse effects such as acute respiratory distress, pneumothorax, barotrauma, dizziness, convulsions or seizures, and visual changes. They also recorded other adverse events as unsolicited. These included inability to equalise middle ear pressures, anxiety, chest pain, nausea, hypo- and hyperglycaemia, wound

			infection, pain after tympanic membrane rupture and congestive heart failure. Fedorko et al. (2016) reported solicited adverse events in 9 HBOT and 6 controls (p=0.44), and unsolicited adverse events in 24 HBOT and 5 controls (p=0.02). This result indicates that HBOT causes a significant number of adverse effects. Safety of HBOT is important to patients.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1.	Freedom from major amputation or meeting the criteria for major amputation	Grade B	Freedom from major amputation or meeting the criteria for major amputation (defined as below-knee or metatarsal level amputation) at 12 weeks, was based on not having any of the following criteria for amputation: 1. Lack of significant progress in wound healing over the follow-up period, which indicated a risk of severe systemic infection related to the wound 2. Persistent deep infection involving bone and tendons (antibiotics and hospitalisation required, pathogen involved) 3. Inability to bear weight on the affected limb 4. Pain causing significant disability. This is a subjective judgement of the presence of indications for amputation, made by a single surgeon, blinded to the participant's treatment allocation. Only Fedorko et al. (2016) reported

			this outcome measure. They reported no effect of HBOT on this outcome in a high quality double-blind trial with 103 participants. They reported that 23% of HBOT and 24% of controls met criteria for major amputation over the 12 weeks of the study. This result suggests that HBOT had no effect on this outcome. The result provides an indication of whether HBOT reduces the risk of a below-knee or metatarsal-level amputation. This would be of major benefit, but the results provide no reason to believe HBOT has this effect.
2.	Recommendation in favour of major or minor amputation	Grade B	This is a subjective judgement of the presence of indications for amputation, made by a single surgeon, blinded to the participant's treatment allocation. Only Fedorko et al. (2016) reported this outcome measure. They reported that 51% of HBOT and 48% of controls were judged to need major or minor amputation over the 12 weeks of the study. The result provides an indication of whether HBOT reduces the risk of a below-knee or metatarsal-level amputation, or a minor amputation of one or more toes. This would be of major benefit, but the results provide no reason to believe HBOT has this effect.
3.	Progress of ulcer healing over 12 weeks	Grade B	Wound size was measured weekly manually and by computerised analysis of wound surface area and perimeter from high-resolution calibrated digital photographs. The authors also calculated the linear advancement of the wound edge. All measurements were made at 12 weeks. This is an assessment of the

			progress and extent of wound healing, made blind to the participant's treatment allocation. Only Fedorko et al. (2016) reported this outcome measure. They reported a difference in mean width reduction of -0.12cm, 95% CI -0.46 to 0.22, p = 0.491. This result suggests that HBOT had no effect on this outcome. Faster wound healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.
4.	Progress of ulcer healing by day 14	Grade B	Average reduction in ulcer area by day 14 was assessed. Ulcer area was assessed by computerised examination of clinical photographs. Only Ma et al.'s (2013) unblinded randomised trial with 36 participants reported this outcome measure. In the HBOT arm, the average reduction in ulcer area was 42%, compared with 20% in the control arm ($p<0.05$). Faster wound healing would be of major benefit; the results suggest that HBOT may hasten this outcome. The assessment was made without blinding to the participant's treatment allocation, increasing the risk of bias.
5.	Progress of ulcer healing as measured by the Bates-Jensen would assessment tool	Grade B	The Bates-Jensen wound assessment tool was used weekly to measure progress of ulcer healing. This is an assessment of the progress and extent of wound healing, made blind to the participant's treatment allocation. This tool assesses 13 wound characteristics, with each item scored on a 1 to 5 scale (maximum score 65). The individual scores

			are summated for a total score. The higher the total score, the more severe the wound status. Only Fedorko et al. (2016) reported this outcome measure. They reported a difference in mean change in score of 0.53, 95% CI -2.58 to 3.64, p = 0.735. This result suggests that HBOT had no effect on this outcome. Faster wound healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.
6.	Proportion of ulcers healed at 12 weeks	Grade B	The proportion of ulcers healed (ie Wagner grade 0 or 1) was measured at 12 weeks. This is an assessment of the progress and extent of wound healing, made blind to the participant's treatment allocation. (The Wagner classification of diabetic foot ulceration is as follows: Grade 0 No open ulcer, high risk; Grade 1 Superficial ulcer with subcutaneous involvement; Grade 2 Deep ulcer with tendon or joint involvement; Grade 3 Deep ulcer with bone involvement; Grade 4 Wet or dry gangrene (forefoot), without cellulitis; Grade 5 Generalized (whole foot) gangrene.) Only Fedorko et al. (2016) reported this outcome measure. They reported that 20% of HBOT and 22% of controls had healed at 12 weeks. This result suggests that HBOT had no effect on this outcome. A higher likelihood of ulcer healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.
7.	Proportion of ulcers healed by	Grade B	Ulcer healed by day 14.

	day 14		This assessment of the completion of wound healing was made by examination of clinical photographs, without blinding to the participant's treatment allocation. Only Ma et al. (2013) reported this outcome measure. They reported no effect of HBOT on this outcome in an unblinded trial with 36 participants. Faster wound healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.
8.	Clinical outcome	Grade B	This outcome measure enumerated how many participants were in each of six clinical categories at the completion of the trial. The categories were: healed (complete closure without debridement in the operating room), graft or flap (graft or flap closure required), distal amputation (amputation distal to metatarsophalangeal joints), proximal amputation (amputation proximal to the metatarsophalangeal joints), debridement (standard therapy wound or operative debridement), no change (failure to heal during the course of treatment). Only Duzgun et al. (2008) reported this outcome measure, in an unblinded trial with 100 participants. Faster wound healing would be of major benefit. The study suggests it may be more likely after HBOT, but was unblinded, so the results may be attributable to observer bias. It is surprising that none of 50 control participants' ulcers were healed after 92 weeks, indicating that the control intervention was ineffective. Since treatment without HBOT usually leads to ulcer

			healing, this result suggests the control treatment was not representative of normal care, reducing the generalisability of the trial's result.
9.	Cost utility	Grade B	This is a measure of costs, outcomes (major amputation, healed with or without a minor amputation, unhealed) and the utility of these outcomes. This result is intended to indicate the cost utility, or health value for money, of HBOT for diabetic foot ulcers. Only Chuck et al. (2008) reported this outcome. They used modelling based on a 2003 study of the effectiveness of HBOT (Guo et al. 2003) and Canadian healthcare cost data. Their modelling indicated that HBOT was more effective and less expensive than standard care. The unreliable assumptions used in this study's model undermine its usefulness to NHS policymakers. The estimates of the effectiveness of HBOT were based on unreliable and potentially obsolete studies, and not compatible with Fedorko et al's (2016) high-quality randomised trial. Also, the costs are based on the Canadian health care system in 2008, and may be materially different from those in the NHS.