CPAG Summary Report for Clinical Panel – URN 1776 - Hyperbaric Oxygen Therapy for Necrotising Soft Tissue Infections

Use of Hyperbaric oxygen therapy (HBOT) plus standard care Vs. standard care to treat necrotising soft tissue infections			
The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is a survival benefit [A]	Mortality is the proportion of participants who die during the study. Soh et al 2014 reported lower mortality with HBOT (adjusted OR 0.45, 95% CI 0.29 to 0.83, p = 0.008). This study indicates that HBOT may reduce mortality, but is subject to bias due to uncontrolled confounding. Mortality reduction would be of high value to patients. Soh et al 2012's analysis suggests that this may be the case, though their study is not robust enough to make this conclusion reliable.
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	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1.	Mean curative time (not defined)	C	Li et al 2015 do not define this outcome measure, but it may be the period from admission to the disappearance of all signs and symptoms of infection. The authors report shorter curative time with HBOT (HBOT: 15.4 days, SD 4.8; control 25.5 days, SD 9.6; $p < 0.05$). These results suggest that HBOT might reduce the duration of illness by about 10 days. Faster cure would be of benefit to patients, though Li et al 2015 do not report shorter length of stay with HBOT.
2.	Mean number of debridements	A	The outcome measure reports the mean number of debridement procedures per participant. Devaney at al 2015 reported more debridements with HBOT: HBOT 4.8 (SD 3.4), control 3 (SD 2.1), $p < 0.001$. This study is more reliable than Krenk et al 2007 because of its multivariate adjustment. This indicates that HBOT is associated with more debridement procedures being carried out. Patients are materially disadvantaged if HBOT leads to more operative procedures being required, unless longer term outcomes are better as a result. However, Devaney et al 2015 was seriously confounded by differences between patient groups. Furthermore, the number of procedures may be a

			confounding variable that affects outcomes.
3.	Mean number of incision and drainage procedures	B	The outcome measure reports the mean number of incision and drainage procedures per participant. Krenk et al 2007 was the only study to report this outcome (HBOT 4.63, control 2.13, $p > 0.05$). This result does not suggest an effect of HBOT on the number of incision and drainage procedures. Patients are materially disadvantaged if HBOT leads to more operative procedures being required, unless longer term outcomes are better as a result. However, this result may plausibly be attributed to chance and is not conclusive. Furthermore, the number of procedures may be a confounding variable that affects outcomes.
4.	Number of amputations	B	The outcome measure reports the mean number of amputations per participant. Devaney et al 2015 was the only study to report this outcome (HBOT 21/275 (7.6%), control 10/66 (15.2%), significance not reported but Yates' χ^2 calculated by SPH as 2.79, $p = 0.095$). This result does not suggest an effect of HBOT on the number of amputation procedures. Patients benefit greatly if HBOT leads to fewer amputations being required. However, this result does not support that conclusion.
5.	Intensive care admission	B	The outcome measure reports the mean number of participants admitted to intensive care. Devaney et al 2015 was the only study to report this outcome (HBOT: 210/275 (76%), control

			37/66 (64%), p = 0.05). This result suggests HBOT is associated with a higher number of intensive care admissions, although this result is of borderline statistical significance. Patients benefit if HBOT leads to fewer intensive care admissions being required. The participants in Devaney et al 2015 who received HBOT had lower APACHE III scores (a severity-of-disease classification system), indicating less severe illness. There are several possible explanations for this finding: HBOT patients were treated more aggressively overall, possibly because clinicians were unblinded or because they were treated by different groups of clinicians; APACHE III is a poor indicator of illness severity in these patients, and those who received HBOT were in fact more seriously ill; HBOT leads to an increased need for intensive care. The study does not enable us to evaluate which of these is correct, though the authors cast doubt on the accuracy of APACHE III.
6.	Days of intensive care unit stay	C	The outcome measure reports the mean number of days for which participants were admitted to intensive care. George et al 2009 was the only study to report this outcome (HBOT 5.7 days (SD 9.1), control 4.7 days (SD 6.7), p = 0.95). This result suggests HBOT has no effect on the duration of intensive care admissions. Patients benefit if HBOT leads to shorter intensive care admissions being required, and costs would be avoided, but there is no evidence from George et al 2009 that this is the case.

7.	Days of antibiotic use	C	The outcome measure reports the mean number of days on which participants received antibiotics. George et al 2009 was the only study to report this outcome (HBOT 18 (SD 12), control 20 (SD 17), p = 0.97). This result suggests HBOT has no effect on the duration of antibiotic treatment. Patients benefit if HBOT leads to shorter courses of antibiotic treatment, and costs would be reduced, but there is no evidence from George et al 2009 that this is the case.
8.	Incidence of complications	B	The outcome measure reports the incidence of complications. Neither study specified the complications, though in the case of Psoinos et al 2013 they were complications of NSTIs rather than of HBOT. Psoinos et al 2013 was the higher quality study reporting this outcome (OR 0.82, 95% CI 0.57 to 1.18). This result suggests HBOT has no effect on the incidence of complications. Patients benefit if HBOT leads to fewer complications, but there is no evidence from Psoinos et al 2013 that this is the case.
9.	Length of hospital stay	A	This outcome measure reports the duration of participants' admissions. The highest quality study was Soh et al 2012 (adjusted analysis: HBOT 14.3 days, 95% CI 13 to 16; control 10.7 days, 95% CI 10 to 11; p < 0.001). This study is more reliable than Psoinos et al (2013) because of more comprehensive multivariate adjustment. This study indicates longer length of stay with HBOT.

			Longer length of stay is disadvantageous to patients and more expensive, unless longer term outcomes are better as a result. Soh et al 2012 reported longer length of stay among survivors, indicating that the difference does not arise because of higher or earlier mortality without HBOT.
11.	Cost	A	This outcome measure indicates the cost of all treatment, including HBOT where this was used. This indicated that treatment with HBOT is more expensive than treatment without. Higher treatment costs mean less funds are available for other patients' care. Soh et al 2012 is a study from the United States and costs in the NHS will differ.

Use of HBOT plus standard care to treat necrotising soft tissue infections (studies with no comparator group)			
The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is no survival benefit [B]	Mortality is the proportion of participants who die during the study. Rosa et al 2015 reported that 19/24 (79%) were discharged alive and 5/24 (21%) died. There was no information on the other 10 participants. These results provide an indication of mortality from one small study. Mortality reduction would be of high value to patients, but this uncontrolled study does not indicate whether it follows HBOT.
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	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1.	Clinical outcome	B	The outcome measure enumerates three possible clinical outcomes (full recovery, survived with amputation, died). Only Bosco et al 2016 reported this outcome measure. They reported the following results from their uncontrolled study: perineal fasciitis: 19/20 (95%) full recovery, 1/20 (5%) died; cervical fasciitis: 8/8 (100%) full recovery; gas gangrene: 6/8 (75%) full recovery, 2/8 (25%) amputation. These results indicate the pattern of clinical outcomes from this study. A greater probability of full recovery would be of high value to patients, but because Bosco et al 2016 was uncontrolled, it provides no indication of whether HBOT makes this more likely.