CPAG Summary Report for Clinical Panel – Recompression with or without Hyperbaric Oxygen Therapy (HBOT) for Decompression Illness/Gas Embolism, URN 1678

Recompression with HBOT alone vs recompression with HBOT plus a non-steroidal anti-inflammatory drug (NSAID) for treatment of decompression illness (DCI)			
The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Choose an item.	
2.	Progression free survival	Choose an item.	
3.	Mobility	Choose an item.	
4.	Self-care	Choose an item.	
5.	Usual activities	Choose an item.	
6.	Pain	Choose an item.	
7.	Anxiety / Depression	Choose an item.	
8.	Replacement of more toxic treatment	Choose an item.	
9.	Dependency on care giver / supporting independence	Choose an item.	
10.	Safety	Adverse events identified [C]	Problems during initial recompression were reported for six out of 179 patients (3.4%) with decompression illness (DCI) treated with recompression (88% according to USN T6) (Bennett et al 2012). Three complained of aural barotrauma (ear discomfort when air pressure changes are experienced), two developed premonitory signs of brain oxygen toxicity and one complained of nausea not resolved by removal from oxygen breathing at depth. This analysis included patients recruited to both the intervention and control arms of a randomised control trial (RCT) designed to evaluate the addition of a Non-steroidal anti-

			inflammatory drug (NSAID), medication widely used to relieve pain, reduce inflammation, and bring down a high temperature) to recompression treatment. The RCT was of reasonably good quality and data were collected prospectively. There was no information on whether these adverse effects of initial recompression had any longer-term impact or on the longer-term outcomes of patients who experienced adverse effects. From the evidence provided by this study it is not possible to determine the significance of adverse effects of initial recompression in patients with DCI.
11.	Delivery of intervention	Choose an item.	

Recompression with HBOT alone vs recompression with HBOT plus a non-steroidal anti-inflammatory drug (NSAID) for treatment of decompression illness (DCI)			
Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1.	Recovery at discharge from hospital	Grade C	Complete recovery at discharge from hospital was defined as 'well, no symptoms or signs'. The overall rate of complete recovery of patients with DCI at discharge was 112/168 (67%) (Bennett et al 2012). The clinical condition of the remaining 33% of patients at discharge was not clear. This analysis included patients recruited to both the intervention and control arms of a RCT designed to evaluate the addition of a NSAID to recompression treatment. No difference in outcomes was found with the addition of the NSAID. All patients received one or more sessions of recompression; 88% had recompression according to USN T6. The RCT was of reasonably good quality and data were collected prospectively. While two-thirds of patients with DCI had recovered at discharge, it is not possible to determine what the contribution of recompression therapy with or without HBOT was to recovery as there was no comparison with patients who did not receive recompression.
2.	Recovery at 4-6 weeks	Grade C	Complete recovery in patients with DCI at 4-6 weeks' follow up was defined as 'well, no symptoms or signs'. It was not stated whether follow up was 4-6 weeks after completion of

			treatment or after discharge. Overall 134/164 (82%) of all patients treated for DCI with one or more sessions of recompression (88% according to USN T6) were reported to have completely recovered at 4-6 weeks (Bennett et al 2012). Longer term outcomes for the remaining 18% are not described. This analysis included patients recruited to both the intervention and control arms of a RCT designed to evaluate the addition of a NSAID to recompression treatment. No difference in outcomes was found with the addition of the NSAID. The RCT was as described previously.
3.		Choose an item.	
4.		Choose an item.	
5.		Choose an item.	

Recompression with or without HBOT for treatment of DCS, DCI or IGE. No comparator			
The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Choose an item.	
2.	Progression free survival	Choose an item.	
3.	Mobility	Choose an item.	
4.	Self-care	Choose an item.	
5.	Usual activities	Choose an item.	
6.	Pain	Choose an item.	
7.	Anxiety / Depression	Choose an item.	
8.	Replacement of more toxic treatment	Choose an item.	
9.	Dependency on care giver / supporting independence	Choose an item.	

10.	Safety	Adverse events identified [C]	Out of 5259 divers with DCI receiving recompression therapy, five were suspected to have developed central nervous system oxygen toxicity and four presented early symptoms of oxygen toxicity (Xu et al 2012). All had been treated with recompression in air with oxygen breathing via face mask, although it was not clear how many of the cohorts had received hyperbaric oxygen. Oxygen breathing was suspended for 30-60 minutes then resumed, after which all were reported to have no recurrence of symptoms. Overall 0.17% of patients in this large cohort were thought to have experienced oxygen toxicity but no longer-term abnormal condition resulting from the previous injury (sequelae) were reported. The treatment schedules used were developed in a Chinese recompression facility and are unlikely to be relevant to the current UK context. Out of 125 patients with IGE, one (0.8%) experienced seizures during HBO, which resolved on shifting from pure oxygen to air (Bessereau et al 2010).
11.	Delivery of intervention	Choose an item.	

Recompression with or without HBOT for treatment of DCS, DCI or IGE. No comparator.			
Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
1.	Outcome immediately after a single HBOT session	Grade C	Outcome after a single HBOT session (US Navy Table 5 or Table 6) (USN T5 or T6)) was described as either complete recovery or residual symptoms in patients with Type I DCS. Overall 33% (n=64) of patients were reported to be completely recovered from Type I DCS and 67% (n=131) to have residual symptoms immediately after treatment (Lee et al 2015). Residual symptoms were reported 'according to the patient's statement'; there were no further details on how these were assessed. From the evidence provided by this study it is not possible to determine the contribution of a single session of HBOT to recovery immediately after treatment in patients with Type I DCS as there was no comparison with patients who did not receive HBOT. In addition, complete recovery and residual

			symptoms were assessed retrospectively and were not defined. The clinical significance of residual symptoms immediately after treatment and their relationship to longer term outcomes is unclear.
2.	Outcome at discharge from hospital	Grade C	Outcomes were described as complete recovery, improvement, ineffectiveness or death at discharge from hospital in 5269 Chinese divers with DCI treated with recompression, of whom around 150 also had additional sessions of HBOT (Xu et al 2012). Complete recovery at discharge was reported in 89.8% (n=4732) of all patients, improvement in 9.5% (n=502), ineffectiveness in 0.2% (n=11) and death in 0.5% (n=24). These findings should be treated with caution as the outcomes were assessed retrospectively and were not defined. It is not possible to determine the contribution of recompression with or without HBOT to recovery at discharge in patients with DCI as there was no comparison with patients who did not receive recompression. The treatment schedules used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.
3.	Outcome one month after treatment with a single HBOT session	Grade C	Self-reported outcomes for patients with Type I DCS who had reported residual symptoms immediately after treatment with one session of HBOT were collected by telephone interview one month after treatment. Overall, of 131 patients with Type I DCS, 92.3% (n=121) reported no symptoms, 6.1% (n=8) residual pain and 1.5% (n=2) having had surgery for shoulder osteonecrosis (Lee et al 2015). The findings should be treated with caution as 'no symptoms' and 'residual pain' were not defined and there were no objective measures of these outcomes. It is not possible to determine from this evidence what the contribution of a single session of HBOT was to recovery one month after treatment in patients with Type I DCS as there was no comparison with patients who did not receive HBOT.
4.	Crude mortality	Grade C	Crude mortality was defined as the proportion of patients who had died at a specified time point after treatment. In a study of 125 patients with gas embolus caused by medical treatment (iatrogenic gas embolus (IGE)) treated with a single session of HBOT, data were collected prospectively and outcomes were reported for 119 patients (6 were lost to follow-up)

			(Bessereau et al 2010). Crude mortality was 12% (14/119) at Intensive Care Unit (ICU) discharge, 16% (19/119) at hospital discharge, 17.6% (21/119) at 6 months and 21% (25/119) at 1 year. This study demonstrates significant mortality in patients with IGE with some deaths occurring more than 6 months after treatment. However it is not possible to determine the impact of HBOT on mortality up to one year in patients with IGE as there was no comparison with patients who did not receive HBOT.
5.	Response to initial recompression for patients with mild, moderate and severe DCI	Grade C	Complete recovery, improvement or ineffectiveness after initial recompression were reported for 5269 Chinese divers with mild, moderate or severe DCI, which was defined, based on symptoms and whether decompression had been omitted (Xu et al 2012). Complete recovery was reported in 92.2%, 81.3% and 48.7% of mild, moderate and severe patients respectively, with a significant association between severity and complete recovery after initial therapy, $p<0.001$. Ineffectiveness was reported in 0%, 0.2% and 4.1% of mild, moderate and severe patients respectively, with a significant association between severity and ineffectiveness after initial therapy, $p<0.001$. The analysis was not clearly described and it is not clear whether there was any adjustment for confounders. From the evidence provided in this study it is not possible to determine what the contribution of initial recompression with or without HBOT was to outcomes after recompression as there was no comparison with patients who did not receive recompression. Patients with more severe disease were reported to have had worse outcomes, but these findings should be treated with caution because severity and outcomes were classified retrospectively, and the outcome groups were not defined. It is also not clear to what extent other confounding factors might have contributed. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.
6.	Condition at discharge for patients with mild, moderate and severe DCI.	Grade C	Complete recovery, improvement, ineffectiveness or death at discharge were reported in 5269 Chinese divers with mild, moderate or severe DCI treated with recompression, of whom around 150 had additional sessions of HBOT. Mild, moderate and severe DCI were defined, based on symptoms and whether decompression had been omitted (Xu et al 2012).

			Complete recovery was reported in 93.8%, 84.8% and 58.9% of mild, moderate and severe patients respectively, with a significant association between severity and complete recovery at discharge, p<0.001. Ineffectiveness was reported in 0%, 0.2% and 2.9% of mild, moderate and severe patients respectively, with a significant association between severity and ineffectiveness at discharge, p<0.001. The analysis was not clearly described and it is not clear whether there was any adjustment for confounders. From the evidence provided in this study it is not possible to determine what the contribution of recompression with or without HBOT was to outcomes at discharge as there was no comparison with patients who did not receive recompression. The relationships between outcome after initial therapy, condition at discharge and long term outcome were not clear. Patients with more severe disease were reported to have had worse outcomes, but these findings should be treated with caution because severity and outcomes were classified retrospectively, and the outcome groups were not defined. It is also not clear to what extent other confounding factors might have contributed. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.
7.	Clinical outcome after completion of treatment for patients with more severe or less severe Type II DCS	Grade C	Clinical outcome (unchanged, improvement or full recovery) after completion of hyperbaric treatments was reported in 267 patients with Type II DCS (Koch et al 2008). The patients were grouped retrospectively by two independent assessors into Type A (more severe) and Type B (less severe) DCS-II according to defined diagnostic criteria. Each outcome group was given a score (unchanged 0, improvement 1, full recovery 2) for the analysis. The mean (+/- SD) outcome score for patients with Type A (n=42) was 1.39 +/-0.56, significantly worse than for patients with Type B (n=225) which was 1.82 +/-0.46 (p<0.001). While a statistical association was demonstrated between patients with more severe Type II DCS and worse outcome scores, it is not possible to comment on the clinical significance of this difference in outcome scores. In addition the findings should be treated with caution as the outcome groups were classified retrospectively and were not defined. Details of treatment schedules were not given or

			referenced, and it is not known whether patients received HBOT. From the evidence provided in this study it is not possible to determine what the contribution of recompression with or without HBOT was to outcomes after completion of treatment for patients with Type II DCS.
8.	Outcomes at one year in relation to patient and treatment factors	Grade C	The odds ratios (OR) of having neurological sequelae and of crude mortality at one year in relation to various patient and treatment factors were reported in patients with IGE treated with a single HBO procedure (Bessereau et al 2010). Data were collected prospectively in 105 patients who survived ICU. Neurological sequelae were not defined but a number of examples were given, such as focal motor deficits, restriction of visual field, and seizures. A significant association on multivariate analysis was found between patients having a positive Babinski sign ($p=0.0007$) or focal motor deficit ($p<0.0001$) at presentation and neurological sequelae at one year. A significant association was also found between patients having a positive Babinski sign at presentation ($p=0.04$) or acute renal failure ($p=0.03$) and mortality at one year. However these came from initial analysis of 34 variables in 102 analyses so should be treated with caution. It is not clear whether analyses were planned beforehand (prior hypotheses were not stated). The clinical relevance of these findings is uncertain as it is not clear to what extent treatment decisions about patients similar to those in this study would be influenced by knowledge of these characteristics. All patients received HBOT and it is not possible from the evidence provided by this study to determine the impact of HBOT on neurological sequelae or mortality at one year in patients with IGE as there was no comparison with patients who did not receive HBOT.
9.	Response to initial treatment with different treatment tables	Grade C	Response to initial treatment, compared to treatment table used, was reported for 536 patients treated for DCI with various treatment schedules (Sayer et al 2009). Patients were retrospectively allocated to one of five outcome groups: no symptoms at start, complete resolution, major improvement, moderate improvement, slight or no improvement. Outcomes were reported for four main groups of treatment schedules, which were used for varying proportions of patients: Royal Navy Table 62 (RN

			T62) (57% of patients), RN T62 with extension (33%), air or helium oxygen saturation (Sat Tx) (4%), and RN T61 or HBO (6%). A higher proportion of the 90% of patients treated with RN T62 were reported to have a better response than those treated with Sat Tx or RN T61/HBO. However there were no measures of the significance of differences between treatment groups. It was unclear how comparable the treatment groups were and to what extent adjustments were made for potential confounders. The outcome groups were not defined and the clinical significance of the outcomes in the immediate or longer term was also not clear; the response to initial treatment was reported to not necessarily relate to outcomes at discharge. From the evidence provided in this study it is not possible to determine the contribution of recompression with or without HBOT, or of recompression using different treatment schedules, to outcomes after initial treatment for patients with DCI.
10.	Recovery 10-14 days after treatment with different treatment tables more than 48 hours after surfacing	Grade C	No improvement, partial recovery or complete recovery were reported 10-14 days after treatment of divers with DCS who received recompression with USN T6 (n=46) or 2ATA (n=27) more than 48 hours after surfacing (Hadanny et al 2015). In patients receiving USN T6 3% had no improvement, 13% partial recovery and 84% complete recovery. In patients receiving 2ATA 14.8% had no improvement, 18.5% partial recovery and 66.7% complete recovery. There was no significant difference between the two treatment groups (p=0.07). A multivariate analysis of clinical outcome for all divers compared with patient and treatment variables was reported to find more favourable outcomes for patients treated with USN T6 (p=0.009). However no further details of this analysis were provided, so it is not possible to judge its reliability or the implications for treatment. The clinical significance of outcomes at 10-14 days and their relationship to longer term outcomes was not described. The findings of this study should be treated with caution as it is not clear how similar the treatment groups were and whether any adjustments were made in this analysis for confounders. The outcomes were assessed retrospectively and were not defined. Around half of all patients received additional HBOT sessions but there was no information on the number, significance or impact

			on outcomes. It is not possible to determine the contribution of recompression with or without HBOT, or of recompression using different treatment schedules, to outcomes 10-14 days after treatment for patients with DCS.
11.	Recovery immediately after a single HBOT session in relation to time to treatment	Grade C	The odds ratio (OR) of residual symptoms immediately after treatment with one session of HBOT, in relation to the time between developing symptoms and receiving treatment, was reported for 195 patients with Type I DCS (Lee et al 2015). Patients who received HBOT up to 24 hours after developing symptoms were treated as the reference group, and in multivariable logistic regression analysis, the OR (95% CI) for residual symptoms by time from symptoms to recompression was: 24-96 hours: 2.24 (0.75-6.65); 96-240 hours: 3.31 (1.08-10.13); ≥240 hours: 23.84 (2.45-231.43). This analysis therefore suggests that patients receiving recompression more than 96 hours after the development of symptoms had a significantly greater chance of residual symptoms immediately after treatment than patients treated within 24 hours. However the clinical significance of residual symptoms immediately after treatment and their relationship to longer term outcomes is unclear. In addition the findings should be treated with caution because patients were allocated retrospectively to outcome groups, which were undefined.
12.	Recovery at discharge in relation to time to treatment	Grade C	Complete or incomplete recovery at discharge, compared with the time between onset of symptoms and receipt of recompression treatment, was reported in 5269 Chinese divers with DCI (Xu et al 2012). A significant association was reported between a longer time between symptom onset and treatment, and higher rates of incomplete recovery ($p<0.0001$). The proportions of patients receiving treatment within different times from symptom onset who had complete/incomplete recovery were: 1-6hrs (n=2559) 93.8%/5.3%; 6-12hrs (n=1802) 87.6%/12.0%; 12-24hrs (n=555) 85.2%/14.4%; 24-36hrs (n=234) 80.8%/18.4%; >36hrs (n=119) 75.6%/24.4%. The evidence from this study suggests that there were worse outcomes at discharge for patients who had a longer time between symptom onset and treatment. However the findings should be treated with caution as complete and incomplete recovery were assessed retrospectively and were not defined. In addition it is not clear to what extent

			the analysis was adjusted for confounders as details of the analysis were not described. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.
13.	Recovery 10-14 days after treatment with early or delayed recompression	Grade C	No improvement, partial recovery and complete recovery 10-14 days after treatment were reported for 204 divers with DCS who received recompression less than 48 hrs from surfacing (early recompression) or more than 48hrs after surfacing (delayed recompression) (Hadanny et al 2015). In early recompression (n=128), 78% had complete recovery, 15.6% partial recovery and 6.2% no improvement. In delayed recompression (n=76) 76% had complete recovery, 17.1% partial recovery and 6.6% no improvement. There was no significant difference between the two groups (p=0.955). In the delayed treatment group 70% had symptom onset within 12 hrs of surfacing. The evidence provided in this study suggests that delay in treatment has no effect on outcome at 10-14 days in patients with DCS. However the findings should be treated with caution as the outcomes were assessed retrospectively and were not defined, and it is not clear how similar the treatment groups were and whether any adjustments were made in this analysis for confounders. The clinical significance of outcomes at 10-14 days and their relationship to longer term outcomes was not described.

Abbreviations

2ATA	2 atmospheres absolute	MSK	Musculoskeletal
AGE	Arterial gas embolus	NSAID	Non-steroidal anti-inflammatory drug
CI	Confidence intervals	OR	Odds ratio
CX30	Comex 30	RCT	Randomised controlled trial
DCI	Decompression illness	RN T61	Royal Navy table 61
DCS	Decompression sickness	RN T62	Royal Navy table 62
DCS-I	Decompression sickness Type I	RN T62 ext	Royal Navy table 62 with extension
DCS-II	Decompression sickness Type II	Sat Tx	Saturation treatment
HBOT	Hyperbaric oxygen therapy	SD	Standard deviation
ICU	Intensive care unit	USN T5	US Navy table 5
IGE	Iatrogenic gas embolus	USN T6	US Navy table 6