CPAG Summary Report for Clinical Panel – Dexrazoxane for preventing cardiotoxicity in people aged under 25 years receiving high-dose anthracyclines or related drugs for the treatment of cancer [URN: 1825]

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	This outcome looked at how many participants were alive at the last follow-up. Because of safety concerns that dexrazoxane may reduce survival in children this is an important safety outcome. A long-term report from 3 randomised control trials (RCTs) (n=1,008) found that, over a median 12.6 year follow-up, there was no significant difference in overall survival rate for dexrazoxane compared with no dexrazoxane. The Hazard Ratio (HR), a measure of an effect of an intervention on an outcome of interest over time, was 1.03 (95% Confidence Intervals [CI] 0.73 to 1.45). These results suggest that dexrazoxane does not reduce overall survival up to 12.6 years after treatment. The impact on overall survival beyond this point is not known.
2.	Progression free survival	This outcome looked at how long a person lives with their disease for without it getting worse. Because of safety concerns that dexrazoxane may reduce survival in children this is an important safety outcome. The systematic review reported that, across 5 RCTs (n=1,254) there was no difference in event-free survival for children and young people treated with dexrazoxane compared with those not treated with dexrazoxane, HR 0.99 (0.78 to 1.25, p=0.91). These results suggest that dexrazoxane does not reduce event-free survival for around 3.3 to 9.6 years after treatment. The event-free survival beyond this point is not known.
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	This outcome looked at how many people had grade 3 (severe) or grade 4 (life-threatening or disabling) adverse effects. The RCT (n=537, median follow-up 9.2 years) reported no statistically significant differences between dexrazoxane and no dexrazoxane in rates of infection, haematological adverse effects and central nervous system (CNS) adverse effects. The RCT found that people treated with dexrazoxane were significantly more likely to have mucositis (52 events) compared with no dexrazoxane (33 events, p=0.02). The following adverse events are reported as being very common (occurring in 1/10 people or more) in the SPC for dexrazoxane: • Anaemia • Leukopenia (low white blood cell count) • Nausea • Vomiting • Stomatitis (a sore or inflammation inside of the mouth) • Alopecia • Asthenia (lack of energy and strength). These results suggest that children and young people treated with dexrazoxane are more likely to have mucositis compared with those not treated with dexrazoxane. Haematological events and infections occurred in people treated with dexrazoxane and those not treated with dexrazoxane.
11.	Delivery of intervention	Not measured

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Clinical cardiotoxicity	This outcome looked at how many people had symptoms of clinical cardiotoxicity, which was defined in the study as

		symptomatic congestive heart failure, use of medication for congestive heart failure, heart transplant or death from cardiac causes. The combined results of 4 RCTs involving 991 children and young people found no significant difference in clinical cardiotoxicity for people treated with dexrazoxane (0 events) compared with no cardioprotection (3 events, risk ratio [RR] 0.24, 95% confidence interval [CI] 0.03 to 2.09, p=0.88). It should be noted that the total number of events occurring during the RCTs was very low, meaning the studies may have been underpowered to detect a difference. The combined results of 8 non-randomised studies involving 741 children and young people found significantly lower rates of clinical cardiotoxicity in people treated with dexrazoxane (7 events) compared with no cardioprotection (35 events). RR 0.29 (95% CI 0.14 to 0.61, p=0.001), number needed to treat (NNT) 13 (95% CI 9 to 22). Results from RCTs suggest that dexrazoxane did not reduce clinical cardiotoxicity over a 3.3 to 9.6 year follow-up. Reductions in cardiotoxicity were seen in people treated with dexrazoxane in non-randomised studies, however this evidence is subject to bias and confounding, and is therefore less reliable. These results should be considered with a degree of caution, since heart failure develops over a much longer time in children compared with adults receiving cancer treatment, meaning a very long follow-up would be required to observe a clinically significant difference in symptomatic heart failure. At the time of final follow-up in these studies participants were in their early 20s, and symptomatic heart failure may not develop for another 20 or 30 years.
2.	All cardiotoxicity (including clinical and sub-clinical)	This outcome looked at how many people had any type of cardiotoxicity, including clinical cardiotoxicity (for example, symptomatic heart failure) and sub-clinical cardiotoxicity (asymptomatic changes in echocardiographic or biochemical measures). The combined results of 4 RCTs involving 990 children and young people found rates of clinical or sub-clinical cardiotoxicity were significantly lower in people treated with dexrazoxane (5 events) compared with no cardioprotection (17 events). RR 0.29 (95% CI 0.13 to 0.64, p=0.003), NNT 41 (95% CI 24 to 157). The combined results of 8 non-randomised studies involving 531 children and young people found rates of clinical or sub-clinical cardiotoxicity were significantly lower in children treated with dexrazoxane (30

		events) compared with no cardioprotection (69 events). RR 0.43 (95% CI 0.30 to 0.63, p<0.001), NNT 7 (95% CI 5 to 12). These results suggest that dexrazoxane significantly reduces the risk of any cardiotoxicity over follow-ups of less than about 9 years, although it should be noted that that the majority of cases were sub-clinical. Surrogate cardiac markers are not yet known to correlate with long-term cardiac dysfunction and cannot be safely used to predict the long-term cardioprotective effect of dexrazoxane
3.	Elevated serum cardiac troponin-T	This outcome looked at how many people had elevated serum cardiac troponin-T. Troponin-T is a protein released when cardiac muscle is damaged and is a marker of cardiac damage. Troponin-T levels above 0.01 nanogram/ml were considered elevated. Across 1 systematic review (including 2 RCTs) and 1 RCT, 20/207 (9.7%) people receiving dexrazoxane had elevated troponin-T levels, compared with 48/190 (25.3%) people not receiving cardioprotection. Rates of raised troponin-T levels was significantly lower for people treated with dexrazoxane in both studies (both p<0.05). These results suggest that people treated with dexrazoxane are less likely to have raised troponin-T levels compared with people not treated with dexrazoxane, meaning they were less likely to have damage to their heart muscle. Troponin-T is a surrogate marker of cardiac damage. Follow-up in all studies was less than 10 years and it is not clear whether such surrogate markers correlate with long-term cardiac dysfunction, for example symptomatic heart failure.
4.	Left ventricular fractional shortening z-score	This outcome looked at left ventricular fractional shortening, reported using z-score. Left ventricular fractional shortening is measured used echocardiography and looks at the degree of shortening of the left ventricular diameter between end-diastole and end-systole. It is used as a measure of the heart's ability to pump blood around the body. A z-score (standard score) expresses deviation from a mean. A z-score of 0 is equal to the mean (a person without cardiac dysfunction). A z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. Across 1 systematic review (including 2 RCTs, n=301), people receiving dexrazoxane had significantly higher (better) z-scores compared with people not receiving cardioprotection. The mean difference (MD) between groups was 0.61 (95% CI 0.22 to 1.01, p=0.002).

		These results suggest that people treated with dexrazoxane are less likely to have left ventricular fractional shortening compared with people not treated with dexrazoxane, meaning their hearts may be working better. Left ventricular fractional shortening is a surrogate marker of cardiac damage. Follow-up in the studies was less than 10 years and it is not clear whether such surrogate markers correlate with long-term cardiac dysfunction, for example symptomatic heart failure.
5.	Left ventricular thickness-to-dimension ratio z-score	This outcome looked at left ventricular thickness-to-dimension ratio, reported using z-score. Left ventricular thickness-to-dimension ratio is measured used echocardiography and is used to predict left ventricular ejection fraction and volume. It is used as a measure of the heart's ability to pump blood around the body. A z-score (standard score) expresses deviation from a mean. A z-score of 0 is equal to the mean (a person without cardiac dysfunction). A Z-score of −1 is equal to 1 standard deviation below the mean, and a Z-score of +1 is equal to 1 standard deviation above the mean. Across 1 systematic review (including 2 RCTs, n=299), children and young people receiving dexrazoxane had significantly higher z-scores compared with those not receiving dexrazoxane. Mean difference between groups 0.66 (95% CI 0.32 to 1.00, p<0.001) These results suggest that people treated with dexrazoxane are more likely to have a lower left ventricular thickness-to-dimension ratio z-score compared with people not treated with dexrazoxane, meaning their hearts may be working better. Left ventricular thickness-to-dimension ratio is a surrogate marker of cardiac damage. Follow-up in the studies was less than 10 years and it is not clear whether such surrogate markers correlate with long-term cardiac dysfunction, for example symptomatic heart failure.
6.	Relapse or disease progression	This outcome looked at how many people experienced a relapse of their cancer or disease progression. Over a 12.6 year follow-up, across 3 RCTs (n=1,008), there was no difference in the number of people having a relapse or disease progression with dexrazoxane (15.6%) compared with no dexrazoxane (19.0%), hazard ratio 0.81 (95% CI 0.60 to 1.08). These results suggest that dexrazoxane does not increase the risk of disease relapse or progression up to 12.6 years after

		treatment. The risk of relapse or progression beyond this point is not known.