**Methods**

1. Why do you think it was necessary to have an ombudsman at each recruiting site? To make sure parents fully understood the trial **2 marks**
2. Why do you think children with abnormal Transcranial Doppler velocity were excluded from the study? Because best current management would be transfusion **2 marks**
3. Why do you think it was necessary to have a placebo control? To control for a placebo effect in the patient and an unconscious (or conscious bias) on the part of the parents **2 marks**
4. What are the disadvantages to using a single dose of hydroxycarbamide? Prevents dose escalation to allow for interindividual differences in disease severity or response (e.g. due to differences in baseline HbF). **3 marks**
5. Why do you think the investigators stopped measuring glomerular filtration rate? Presumably ‘statistically futile’ means the results between placebo and treatment were so close that no difference was likely to emerge and the children are being exposed to a small doe or irradiation and the procedure is relatively costly. **2 marks**
6. Was the study large enough to address the study endpoints? Yes, it was calculated to be large enough But actually they didn't recruit enough patients since they calculated they needed 100 in each arm and only ~80 were recruited and completed the study. **2 marks**

**Results**

1. What are the main effects of hydroxycarbamide on haematological values? Increased Hb, HbF and MCV, reduced WBC, neutrophils and reticulocytes. **3 marks**
2. What laboratory tests are likely to provide the best evidence of good compliance with trial medication? MCV, WBC, neutrophils, Hb, Hb F, reticulocytes all differed. Absolute reticulocyte count showed the most significant difference**. 2 marks**
3. What significant new information is provided by this trial? That hydroxycarbamide in children with sickle cell disease aged 9 months to 2 years has similar haematological and clinical effects to those in older patients and has no unexpected toxicity. **2 marks**
4. What factors would be most useful in deciding whether or not hydroxycarbamide treatment is cost-effective? Reduced number and duration of hospital admissions. **2 marks**
5. What do you think are the main limitations of this trial? Single dose of hydroxycarbamide. It could be useful to know if some of the excluded groups would also benefit. Glomerular filtration rate may not be the most relevant renal measurement at this young age. Loss of concentrating ability might be something that happened earlier. Main problem is the very short follow up given that this is a trial to prevent chronic organ damage and these are very young children**. 3 marks**

**Final conclusion 5 marks**

1. Do you think this study will change clinical practice and if so, why?

Very little impact on clinical practice in the short-term until longer term follow up shows whether or not there is any benefit associated with treating asymptomatic children. This is because they don't make a convincing case that hydroxycarbamide prevents chronic organ damage; this is the main issue because hydroxycarbamide is used for symptomatic sickle cell disease but these patients were not selected to be symptomatic, i.e. they exposed asymptomatic young children to the toxicity of hydroxycarbamide without measurable long -term gain. So the only effect on practice has been (and at this stage will be because of the short follow up) that if very young children are symptomatic, hydroxycarbamide is fairly safe. Primary endpoints were retaining splenic function and renal function. There was no difference in these. There were many secondary endpoints but neither the primary nor secondary endpoints included pain, acute chest syndrome, dactylitis etc. even though these things were analysed.