CPAG Summary Report for Clinical Panel – Ustekinumab for refractory Crohn's disease in children and young people (8061)

The Benefits of the Proposition – ustekinumab for refractory Crohn's disease in children and young people – no comparator in study			
No	*Outcome measures*	*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 [C]	This outcome looked at how many children and young people had adverse events while they were having ustekinumab for refractory Crohn's disease. Rate of adverse events: 12.4 per 1000 patient-months of follow-up. 4.5% (2/44) had a serious adverse event after receiving 1 induction dose: perianal abscess in 1 participant and worsening of chronic recurrent osteomyelitis (bone infection) and psoriasis in the other participant.

			14.3% (6/42) participants had mild adverse events during the maintenance phase of treatment: 2 participants reported migraine after 1 and 3 months on treatment, 2 participants reported flares of scalp psoriasis, 1 participant reported non-persistent bilateral feet paraesthesia (a burning or prickling sensation) after 3 months on treatment and 1 participant reported chronic rhinitis symptoms. These results are from a small, uncontrolled study which is at risk of bias and other influencing factors in the study population. Only 32 children and young people had ustekinumab treatment for at least 12 months. There was no comparator in the study, so it provides no information on the safety and tolerability of ustekinumab compared with other treatments. The induction regimens varied between and within the study centres and were different to the induction regimen for the licensed indication for Crohn's disease in adults. For the treatment of Crohn's disease in adults ustekinumab is given as an intravenous infusion for the first dose, subsequent dosages are then given as subcutaneous injections. In the study a subcutaneous injection induction regimen was used. Therefore, this study does not provide any information on the intravenous infusion ustekinumab formulation in children and young people. Based on the limited data from the study it is difficult to draw firm conclusions on the safety and tolerability of ustekinumab for the treatment of refractory Crohn's disease in children and young people.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review			
No	Outcome measure	Grade of evidence	Summary from evidence review

1.	Clinical remission	Grade C	This outcome looked at how many children and young people had their Crohn's disease in clinical remission (symptoms have subsided and are under control) at 3 and 12 months after starting ustekinumab treatment. Crohn's disease symptoms were measured using the same validated scale in all participants (the abbreviated paediatric Crohn's disease activity index (PCDAI), clinical remission was defined as a score of less than 10 on this scale). 36.4% (16/44) were in clinical remission at 3 months and 38.6% (17/44) were in clinical remission at 12 months (results were statistically significant). This suggests that ustekinumab was effective at bringing refractory Crohn's disease under control in approximately 36% of the children and young people after 3 months treatment. After 12 months treatment, approximately 39% had their Crohn's disease under control. It is unclear from the study if it was the same 16 participants in remission at 3 months that were still in remission at 12 months. Four participants were in clinical remission at baseline before ustekinumab was started, it is not clear if these participants were still in remission at 3 and 12 months. These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and influence of other factors in the study population, it is difficult to interpret and cannot support firm conclusions. There was no comparator in the study, so it provides no information on clinical effectiveness of ustekinumab compared with any other treatment. The ustekinumab induction regimens varied

			within and across the study centres. The induction regimens used in this study in children and young people were different to the induction regimen for the licensed indication for the treatment of Crohn's disease in adults.
2.	Steroid-free clinical remission	Grade C	This outcome looked at how many children and young people had their Crohn's disease in clinical remission and in addition were not taking steroids 12 months after starting ustekinumab treatment. 27.3% (12/44) were in steroid-free clinical remission at 12 months (no statistical analysis provided). Steroid exposure was only measured in the 32 participants who remained on ustekinumab for at least 12 months. 40.6% (13/32) were taking steroids at baseline and 15.6% (5/32) were taking steroids at 12 months (not statistically significant). This suggests that just over a quarter of the children and young people had their Crohn's disease in remission and in addition were not taking steroids 12 months after starting treatment with ustekinumab. Among those who continued ustekinumab treatment for at least 12 months there was no statistically significant difference between the number taking steroids at baseline and the number taking steroids at 12 months. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as

			described above under the clinical remission outcome. The small size of the group that continued ustekinumab for at least 12 months may mean that it was not sufficiently powered to detect a difference between the number taking steroids at baseline and 12 months.
3.	Clinical response	Grade C	This outcome looked at how many children and young people had an improvement in their Crohn's disease symptoms. Crohn's disease symptoms were measured using the same validated scale in all participants (clinical response was defined as a decrease in abbreviated PCDAI score of 15 or more, on this scale lower scores are better). 47.8% (21/44) had a clinical response at both 3 and 12 months (no statistical analysis provided in study). This suggests that just under half of the children and young people had some improvement in their Crohn's disease symptoms with ustekinumab treatment. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome.
4.	Number of participants who required surgery	Grade C	This outcome looked at how many children and young people had surgery during the follow-up period. Participants in the study were followed-up for at least 12 months or until the ustekinumab was stopped. The average follow-up period in the study was not reported. 9.1% (4/44) required surgery during the follow-up period, it was not reported what the surgery was. Two of the 4 participants continued ustekinumab treatment after surgery. This suggests that some children and young people with refractory Crohn's disease treated with ustekinumab may still require surgery.

			These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. It is also not clear from the study whether the reason for surgery was because of the Crohn's disease or a complication related to this.
5.	Change in height, weight and BMI z-scores between baseline and 12 months	Grade C	This outcome looked at changes in height, weight and BMI between baseline and 12 months after starting treatment with ustekinumab, using the z-score. A z-score expresses deviation from a mean (average). A z-score of 0 is equal to the mean (for height, weight or BMI for a child or young person at a specific age and gender). 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. Z-scores based on WHO growth chart standards were used. At baseline, the median z-score for height was −0.68, for weight it was −0.61 and for BMI it was −0.66. At 12 months, the median z-score for height was −0.82, for weight it was −0.05 and for BMI it was 0.18. The mean increase in height z-score was 0.072 (not statistically significant). The mean increase in weight z-score was 0.48 (statistically significant) and the mean increase in BMI z-score was 0.66 (statistically significant). This suggests that there was an increase in the average weight and BMI. However, the average height for the group remained lower than reference average heights. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome.

6.	Proportion in whom C reactive protein returned to normal levels	Grade C	This outcome looked at how many children and young people with a raised C reactive protein at baseline had their C reactive protein return to normal levels with ustekinumab treatment. C reactive protein is an inflammatory marker in the blood, that is often measured to check for active inflammation. 30 participants had raised C reactive protein at baseline, this returned to normal in 33.3% (10/30) at 3 months and 26.7% (8/30) at 12 months (results were statistically significant). This suggests that for those who had a high C reactive protein at baseline, for a third this returned to normal after 3 months and for just over a quarter it returned to normal after 12 months with ustekinumab treatment. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. The clinical significance of this outcome is unclear, approximately 32% (14/44) had a normal C reactive protein level at baseline before ustekinumab was started.
7.	Change in albumin levels between baseline and 3 and 12 months	Grade C	This outcome looked at the change in albumin levels from baseline to 3 and 12 months after ustekinumab was started. Albumin is a protein in the blood. Albumin may be low in some people with Crohn's disease because of malnutrition due to poor oral intake or increased loss of protein through the gastrointestinal tract. The normal reference ranges for albumin used in the study were not provided. Median (a way of measuring the average) albumin levels were: 34.5 g/litre at baseline, 36.7 g/litre at 3 months and 40.2 g/litre at

			12 months. Average increase in albumin was 2.7 g/litre from baseline to 3 months and 5.3 g/litre from baseline to 12 months (these results were statistically significant). These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. The clinical significance of these changes in the albumin levels is unclear.
8.	Discontinuation during maintenance phase	Grade C	This outcome looked at how many children and young people stopped having ustekinumab during the maintenance phase of treatment. 30.9% (13/42) stopped ustekinumab during the maintenance phase of treatment. Median time to stopping treatment was 13 months. In all participants treatment was stopped during the maintenance phase because of poor clinical response. This suggests that approximately 31% of children and young people stopped ustekinumab treatment during the maintenance phase. Treatment was stopped because it did not help to control the Crohn's disease. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and due to weaknesses in the study design as previously described.