CPAG Summary Report for Clinical Panel – Rituximab for the treatment of refractory Systemic Lupus Erythematosus (SLE) in adults and children

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	All-cause mortality refers to any death that occurred during the trial. Based on three low quality randomised controlled trials (RCTs). (n=420), Shamliyan et al (2017) reported that there was no difference in all-cause mortality between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE with or without lupus nephritis (LN):SLE (1 RCT, n=257) at 52 weeks: relative risk (RR) 2.1 (95% CI 0.2 to18.4) and LN (2 RCTs, n=163) at 52 to 78 weeks: relative risk[1] (RR) 4.9 (95% confidence interval (CI) 0.2 to 99.6) Survival is of high value to patients. However, it does not indicate a cure and is not a measure of disease activity or patients' symptoms. The results suggest that SLE patients treated with adjunctive rituximab are at no greater risk of mortality from any cause than those treated with standard therapy alone. These results need to be interpreted with caution as they are from a low RCT.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	Adverse events (AE) were not specifically defined by Shamliyan et al (2017) or Alshaiki et al (2018). However, the World Health Organisation (WHO) defines

[1] RR – relative risk (the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group)

		an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention in this case standard treatment for SLE and rituximab. Alshaiki et al (2018) reported that in patients with refractory SLE, infections (four case series), acute or delayed infusion reactions (two case series), thrombocytopenia (one case series), sepsis-like syndrome (two case series) and serum sickness-like reactions (one case series) were reported. However, no other details provided. Shamliyan et al (2017) reported that there was no difference in adverse effects leading to treatment discontinuation between adjuvant rituximab and standard treatment alone in refractory SLE without LN (one RCT, n=257) at 52 weeks [RR 0.8 (95% CI 0.4 to 1.5)] and refractory SLE with LN (one RCT, n=144) at 78 weeks [RR 0.3 (95% CI 0.0 to 3.0)]. They found no difference in serious infections between the treatment arms in patients with refractory SLE at 52 weeks [RR 0.3 (95% CI 0.1 to 2.0)]. They also reported no difference in any infection or total adverse events at 78 weeks in patients with refractory LN based one RCT (n=144) [RR 0.9 (95% CI 0.8 to 1.1)] and [RR 1.03 (95% CI 0.97 to 1.09)] respectively. The BILAG-BR analysis by McCarthy et al (2017) reported 185 infectious episodes in 82 patients during a nine month period. Fifty-four patients suffered multiple infections and 29 (11%) serious infections occurred in 26 patients. The most common infections were respiratory (n = 88) and urinary tract infections (n = 36). At three months, 111 (60%) infections occurred while 60 (32%) infections occurred between three and six months and14 (8%) occurred between six and nine months. Both Alshaiki et al (2018) and McCarthy et al (2017) reported that infections were the most common adverse events. Shamliyan et al (2017) reported no significant differences in the occurrence of adverse events between the study arms. The most common adverse events were infections which are transient however details and/or p values were not reported. Prevention of adverse events is likely to be valued by patients, as they can be serious and/or require hospitalisation. The results suggest that the adverse effect profile of adjuvant rituximab is similar to that of standard treatment alone and that the most common adverse events were transient infections. The results need to be interpreted with caution as no clear description of the numbers or p-values were reported. In addition, they are from a low quality RCT and therefore may not be generalisable. In addition the results reported by Alshaiki et al (2018) and McCarthy et al (2017) were not comparative, it is therefore unclear how this compares to standard treatment alone.
11.	Delivery of intervention	

No	Outcome measure	Summary from evidence review
1.	Global/Overall response	Global or Overall response refers to any response to treatment. This was defined in the systematic review by Shamliyan et al (2017) as partial or complete response. Alshaiki et al (2018) reported global response rates based on three case series that enrolled 57 LN patients and four studies with 206 SLE patients. The pooled global response rates among LN and SLE patients were 70% (95% CI 55% to 81%) and 73% (95% CI 67% to 78%), respectively. No p values were reported and these were not

		comparative results. The two RCTs (n=401) assessed by Shamliyan et al (2017) that reported on overall response found no difference between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 1.0 (95% CI 0.7 to 1.6)] or with LN [RR 1.2 (95% CI 0.9 to 1.7)] at 52 weeks or those with LN at 78 weeks follow-up [RR 1.3 (95% CI 0.9 to 1.7)]. Global or overall response refers to any response to rituximab treatment; it is not an indication of mild disease or cure, just an improvement in disease activity. This is likely to be valuable to patients with refractory SLE. It is not entirely certain what these results mean for the patients with refractory SLE as Alshaiki et al (2018) suggest that about 70% of patients with refractory SLE will have some response (either complete or partial) when rituximab is added to standard treatment. On the contrary, Shamliyan et al (2017) suggests that adjunctive rituximab does not make a difference to overall response in patients with refractory SLE compared with standard treatment alone. These results however should be interpreted with caution as the meta-analysis by Alshaiki et al (2018) included non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors.
2.	Complete response/remission	Complete response was not defined by Alshaiki et al (2018). However, Duxbury et al (2013) defined complete response as the absence of British Isles Lupus Assessment Group (BILAG) A or B scores. Alshaiki et al (2018) reported data on complete remission based on 28 studies - case series and one RCT. Of these, 17 studies (n=773 patients) were on refractory SLE, 10 (n=223 patients) on LN, and one study enrolled 10 patients with neuropsychiatric SLE (NPSLE). The pooled complete response rate was 46% (95% CI, 38% to 55%) in SLE patients, 51% (95% CI 34% to 68%) in LN patients and 90% (95% CI 53% to 99%) in NPSLE patients. No p values were provided. Complete response indicates a valuable effect of treatment however it does not indicate cure. The results suggest that adding rituximab to standard treatment increases the complete response rate in patients with refractory SLE with or without LN. However, it is unknown how the intervention compares to standard treatment alone. It is difficult to interpret these results because the outcome was not defined and may have been subject to inter-study and/or inter-assessor differences and individual interpretation. This is particularly noteworthy as the results were based on 28 studies (mostly non-comparative studies). These clinical benefits suggested by this systematic review may not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment.
3.	Major clinical response	Major clinical response refers to the presence of minimal disease activity, defined in the systematic review by Shamliyan et al (2017) as achieving BILAG C scores or better in all organ systems at week 24

		and maintaining this response without a flare to week 52. A major clinical response, defined by McCarthy et al (2017) as BILAG-2004 C/D/Es only with SLEDAI-2K ≤4 and daily oral glucocorticoid (prednisolone)dose ≤7.5 mg Shamliyan et al (2017) reported that there was no reported difference in major clinical response at 52 weeks between immunosuppressive agents plus rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 0.8 (95% CI 0.4 to 1.5)]. This is based on one RCT (n=257) McCarthy et al (2017) reported that major clinical response was achieved in 33 (18.4%) of patients at six months follow-up. Major clinical response indicates a valuable effect of treatment although this does not indicate cure in patients with refractory SLE. The results reported by Shamliyan et al (2017) suggest that adjunctive rituximab is not beneficial in improving major clinical response while the analysis by McCarthy et al (2017) suggests that this outcome is achieved in less than a fifth of patients with refractory SLE. These results should be interpreted with caution as they were from an RCT deemed to be of low quality by the authors of the systematic review and non-comparative analysis.
4.	Partial response	Partial response is defined in the systematic review by Shamliyan et al (2017) as follows: 1. achieving total BILAG C scores or better at week 24 and maintaining this response for 16 consecutive weeks; 2. achieving no more than 1 organ with a BILAG B score at week 24 without worsening remaining organs to week 52; or 3. achieving a maximum of 2 BILAG B scores at week 24 without developing BILAG A or B scores in new domains until week 52. Alshaiki et al (2018) reported partial response to rituximab based on 25 case series; nine on LN and 16 on refractory SLE (N=928). The number of patients for the individual indications was not given. The pooled partial response rates were 27% (95% CI 18% to 39%) and 34% (95% CI, 28% to 40%) for LN and SLE respectively. No p values were reported and these were not comparative results as they were based mainly on non-comparable studies. Shamliyan et al (2017) on the other hand found that there was no difference at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 1.4 (95% CI 0.7 to 2.6)] based on one RCT (n=257). Partial response indicates an improvement in disease activity in refractory SLE patients. This could be maintaining minimal disease activity short term, moderate disease activity for slightly longer or a combination of these in different organs. Although this is not a cure it is likely to be of some value to patients with consistent active disease. The results reported by Alshaiki et al (2018) suggest that rituximab increases partial response rates in patients with refractory SLE with and without LN. Whereas the results by Shamliyan et al (2017) suggest that adjunctive rituximab is not beneficial in improving partial response in patients with refractory SLE compared with standard treatment alone. These results however should be interpreted with caution as the meta-

		analysis by Alshaiki et al (2018) included non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors.
5.	Change in BILAG score	The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity. Total BILAG score is obtained by combining the scores from all affected organs using the numerical scoring of the BILAG-2004 of A = 12, B = 8, C = 1, and D and E = 0 Pooled results from four case series (number of patients was not reported) by Alshaiki et al (2018) showed that BILAG score was significantly reduced in both LN [mean difference -10 95% CI (-4.37 to -15.63), p<0.001] and SLE [mean difference -10.16 (95% CI -8.36 to -11.97), p<0.001] patients after rituximab therapy. The BILAG-BR analysis by McCarthy et al (2017) also reported that Primary response[2] in terms of BILAG score was achieved in 91 (51%) and 88 (49%) patients at 3 and 6 months respectively. The median (IQR) BILAG-2004 global score at baseline (n=109) was 15 (10 to 23), 4 (2 to 13); p<0.001 at 3 months (n=70) and 3 (2 to12); p<0.001 at 6 months (n=56). Primary response in terms of BILAG score indicates the loss of A (very active disease) scores and B (moderate disease activity) scores in one or no organs. The absence of active or moderate disease activity is likely to be valuable to patients with refractory SLE although it is not a cure. The results suggest that adding rituximab to standard treatment improves the BILAG scores in patients with refractory SLE with or without LN. However, it is unknown how the intervention compares to standard treatment alone. The clinical benefits reported by this systematic review need to be interpreted with caution as the meta-analysis only included non-comparative studies for this outcome which means that the comparative efficacy of adjunctive rituximab compared to standard treatment alone is unknown.
6.	Change in SLEDAI score/low disease activity	SLE disease activity index (SLEDAI) scores are used to assess disease activity and response to treatment. It is a global index that evaluates disease activity over the previous 10 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and haematological. The maximum score is 105. Pooled results from four case series (number of patients was not

[2] Primary definition of response is loss of all A and B BILAG scores to ≤1; B score with no new A/B scores in other organ domains at 6 months

		reported) by Alshaiki et al (2018) showed that SLEDAI score significantly decreased from baseline in both LN [mean difference -10.59 (95% CI -9.40 to -11.78) p<0.001] and SLE [mean difference -6.90 (95% CI -4.17 to -9.63), p<0.001] patients after rituximab therapy. The BILAG-BR analysis by McCarthy et al (2017) also reported that 129 (72.5%) and 128 (71.9%) patients had a reduction in SLEDAI-2K of greater than one point at three and six months follow-up respectively. The median (IQR) SLEDAI-2K reduced from 8 (5 to12) at baseline to 4 (2 to 8); p<0.001 at 3 months and 4 (0 to 7) p<0.001] at six months .Shamliyan et al (2017) found that there was no difference in low disease activity at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with SLE [RR 1.14 (95% CI 0.96 to1.36)] based on one RCT (n=257). However, they reported a significant difference in low disease activity without subsequent flares [RR 1.41 (95% CI 1.02 to 1.95), NNT=7]. SLEDAI is a measure of disease activity therefore a reduction in scores is likely to be valuable in patients with refractory SLE. The results reported by Alshaiki et al (2018) and McCarthy et al (2017) suggest that rituximab reduces diseases activity in patients with refractory SLE. Those reported by Shamliyan et al (2017) suggest that adding rituximab to standard treatment is not better than standard treatment alone in terms of reducing disease activity however it appears to be more effective in preventing subsequent flares. These results however should be interpreted with caution as the both the analysis by McCarthy et al (2017) and the meta-analysis by Alshaiki et al (2018) were based on non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors.
7.	Change in steroid use post therapy	Change in steroid use post therapy refers to any change in the dose of corticosteroids that occurred at study follow-up. Alshaiki et al (2018) reported that pooled mean difference from five case series (number of patients was not reported) showed that prednisolone dose (mg/d) was significantly decreased from baseline in both LN [mean difference -12.50 (95% CI -6.36 to -18.64), p<0.001] and SLE [mean difference -22.93 (95% CI -0.01 to -45.88), p<0.001] patients after rituximab therapy. The BILAG-BR analysis also reported a reduction from baseline in prednisolone dose at six months follow-up (n=149). The median dose reduced from 11.25mg (8.375 to 20 mg) to 7.5mg (5 to 12 mg) p<0.001 (McCarthy et al 2017). A reduction in the dose of steroids required is likely to be valuable to patients with refractory SLE particularly as long term steroid use is associated with organ damage. The results suggest that adding rituximab to standard treatment benefits patients with refractory SLE in terms of taking lower doses of steroids. However, it is unknown how this compares with standard treatment alone. The clinical benefits reported by this systematic review need to be interpreted with caution as the results were based on non-comparative studies for this outcome which means that the comparative efficacy of adjunctive rituximab compared to standard treatment only is unknown.

8.	Change in proteinuria	Proteinuria identifies patients with renal damage and those at risk for worsening renal disease and increased cardiovascular morbidity. Proteinuria is the principal urinary biomarker for the screening of LN and for monitoring disease progression. Urine protein to creatinine ratio (UPC) assay is used typically to diagnose proteinuria and monitor patients with established proteinuria. Four case series (number of patients was not reported) included in the meta-analysis by Alshaiki et al (2018) reported on the change of proteinuria. Pooled results from these studies showed a significant decline in proteinuria from baseline was in SLE patients (mean difference -2.40 (95% CI -1.39 to -3.42) p<0.001]. However, these studies failed to show a significant decrease proteinuria from baseline in LN patients [mean difference -2.52 (95% CI 0.22 to -5.27) p=0.07]. On the contrary, based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant reduction in proteinuria demonstrated by a ≥50% reduction in UPC ratio at 78 weeks compared with standard treatment alone in patients with LN [RR 1.31 (95% CI 1.01 to 1.69), numbers needed to treat -NNT=6)] although this was not the case at 52 weeks. Proteinuria indicates renal damage therefore a reduction is likely to be a valuable treatment effect in patients with refractory SLE. The results reported by Alshaiki et al (2017) suggest that rituximab therapy reduces proteinuria in refractory SLE but not in LN. Those from one RCT included in the systematic review by Shamliyan et al (2017) suggest that adding rituximab to standard treatment may offers some benefit in reducing proteinuria compared to standard treatment in patients with refractory LN. These results however should be interpreted with caution as the meta-analysis by Alshaiki et al (2018) included non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors
9.	Complete renal response	Complete renal response was defined in the systematic review by Shamliyan et al (2017) as the presence of normal serum creatinine level, inactive urinary sediment, and UPC ratio <0.5. One RCT (n=144) included in the systematic review by Shamliyan et al (2017) reported no difference in complete renal response at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with LN [RR 0.9 (95% CI 0.5 to1.5)] Complete renal response indicates significant improvement in renal function; this is likely to be a very valuable treatment effect in patients with SLE particularly those with LN. The results suggest that adding rituximab to standard treatment makes no difference in increasing complete renal response compared to standard treatment in patients with refractory LN. These results need to be interpreted with caution as they are from a low quality RCT and therefore may not be generalisable.
10.	Partial renal response	Partial renal response was defined in the systematic review by Shamliyan et al (2017) as a reduction in serum creatinine level to

		≤115% of baseline, the presence of inactive urinary sediment and at least a 50% decrease in the UPC ratio. Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant improvement in partial renal response at 52 weeks compared with standard treatment alone in patients with LN [RR 2.00 (95% CI 1.05 to 3.82) NNT=7]. Partial renal response indicates some improvement in renal function; this is likely to be of some value in patients with SLE particularly those with LN. The results suggest that adding rituximab to standard treatment offers some benefit in improving renal response compared to standard treatment in patients with refractory LN. These results need to be interpreted with caution as they are from a low quality RCT and therefore may not be generalisable.
11.	BILAG renal domain Improvement	Renal BILAG scores are used to assess disease activity and response to treatment specifically in the kidneys. The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity. Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant improvement in renal BILAG score at 52 weeks compared with standard treatment alone in patients with LN [RR 1.4 (95% CI 1.1 to 1.8) NNT=5]. Change in renal BILAG scores gives an indication of disease activity in the kidneys. An improvement is likely to be a valuable treatment effect in patients with refractory SLE particularly those with LN. The results suggest that adding rituximab to standard treatment offers some benefit in improving renal BILAG compared to standard treatment in patients with refractory LN. These results need to be interpreted with caution as they are from a low quality RCT and therefore may not be generalisable.