CLINICAL PRIORITIES ADVISORY GROUP
03 08 2022

Agenda Item No	
National Programme	Blood and Infection PoC
Clinical Reference Group	HIV
URN	2103

Title
Rituximab for the treatment in acute Thrombotic Thrombocytopaenic Purpura (TTP) and elective therapy to prevent TTP relapse (adults and children aged 2 years and above)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
For routine commissioning The policy proposition is focused on rituximab as a treatment in acute TTP and elective therapy to prevent TTP relapse within the criteria set out in this document. The off-label use of rituximab for prevention and acute treatment of TTP is long established, being commissioned by CCGs as standard of care since 2005. This proposition is intended to formalise the established treatment pathway. TTP is a rare, potentially life-threatening condition that involves blood clots in the small blood vessels in the body (acute thrombotic microangiopathy (TMA)). TTP happens when platelets (type of blood cell that forms blood clots) stick together too readily. Platelets use a highly adhesive glue called von Willebrand Factor (vWF) to form a clot. The size of the vWF determines how easily platelets stick together and if the vWF becomes too long, platelets stick together even when they're not supposed to. **About current treatment** **Rituximab as treatment in acute immune TTP** Treatment of acute immune TTP is with both: • Urgent plasma exchange (PEX) – to replace blood plasma with new plasma fluid in order to replenish stocks of ADAMTS13.

- Immunosuppression – to switch off the immune system response destroying the ADAMTS13 in the blood. Immunosuppression is with high dose steroids initially and rituximab.

Early administration of rituximab during acute episodes reduces time to remission and rituximab should be started within 72 hours of diagnosis. On average, inpatient stay is 14 days and treatment continues as an outpatient, aiming to normalise ADAMTS13 activity.

Rituximab as elective therapy to prevent TTP relapse

Rituximab is used to prevent relapse in patients with a fall in ADAMTS13 activity and symptoms based on the patient's relapse history. The target is normalisation of ADAMTS13 activity as above.

As an elective therapy to prevent TTP relapse, rituximab is also given to the rare group of immune TTP patients who go into clinical remission (no active disease activity) after an acute episode but have persistent ADAMTS13 deficiency (lack) <10% despite having received rituximab and other immunosuppression for the acute episode.

The funding for this drug was agreed by CPAG in January 2020, when the commissioning of the TTP service was agreed. This policy is proposed as an in-year service development.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition

2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the clinical effectiveness and safety of prophylactic rituximab compared with no rituximab?
AND
In people diagnosed with acute immune TTP, what is the clinical effectiveness and safety of rituximab compared with no rituximab?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Mortality **Certainty of evidence: Not applicable**	Mortality from the acute episode is usually the gold standard for assessing survival benefit of drug treatments. Mortality at 3 months after an acute TTP episode is a critical outcome. This outcome is important to patients because acute TTP is a serious, potentially life-threatening condition.
	Prophylaxis Not applicable
Certainty of evidence: Very low	**Treatment** In total five studies (1 SRMA, 3 comparative cohort studies and 1 case series) reported mortality from the acute episode (timepoint not reported). 1 study compared mortality in people with idiopathic TTP and either no response or a disease exacerbation during intensive TPE, 1 study was in people with relapsed or refractory TTP, and 2 studies were in acute de novo or relapsed TTP. • 1 SMRA (Owattanapanich et al 2019) reporting 6 cohort studies (n=362) with follow-up ranging from 1 year to 4 years presented ORs with 95% CIs crossing the line of no effect in all studies, showing no evidence of a difference in mortality (meta-analysis not carried out). **(VERY LOW)** • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) reported mortality in 1/22 (4.5%, day 15) treated with rituximab and in 4/57 (7.0%, mean 8.5 days, SD 1.9) with no rituximab (p value not reported) (median follow-up of survivors: rituximab 33 months (SD 17.4); no rituximab 35.3 months (SD 28.5)). **(VERY LOW)** • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) showed no statistically significant difference in mortality in people

	treated with rituximab (3%) compared with no rituximab (8%), p=0.83 (median follow-up rituximab 3.8 years (IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1)). **(VERY LOW)** • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (n=80) reported mortality in 3/40 (7.5%,11 to 25 days after admission) participants treated with rituximab and in 3/40 (7.5%, 2 during admission, 1 on relapse) participants with no rituximab (during 1 year follow-up) (p value not reported). **(VERY LOW)** • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) provided non-comparative evidence that of 104 patient episodes (in 86 patients) 6 (5.8%) patients treated with rituximab died, after a median of 12.5 days (range 4 to18) from admission (median follow-up 45 months (range 4 to 100 months)). **(VERY LOW)** **These studies provided very low certainty evidence. They did not provide evidence that there is a difference in mortality from the acute episode after treatment with rituximab compared with no rituximab. Fewer people in rituximab groups died than in no rituximab groups overall across studies, but none of the studies reported that there was a statistically significant difference in mortality.**
Relapse rate **Certainty of evidence: Very low**	Relapse rate is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. Relapse rate from an acute TTP event is best measured over 2 years, during which time most relapses will occur. **Prophylaxis** In total, four studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported evidence relating to relapse rates measured at different time points from 15 months to 38 months. Three studies compared results for relapse measures between people treated with rituximab and people not treated with rituximab. Details of the types of comparator treatments were not described in the comparator studies. At median 5 months follow up (pre-emptive rituximab) • 1 case series (Westwood et al 2017) (n=76 patient episodes) provided non-comparative evidence that relapse (readmission with thrombocytopenia with or without new symptoms 30 days after discharge from an

	acute episode) occurred in 3/76 (3.9%) patient episodes. **(VERY LOW)** Re-treatment with rituximab was given in 38/76 (50%) of patient episodes and the rate of re-treatment episodes per year was 0.25 **(VERY LOW)** At median 36 to 38 months follow up (pre-emptive rituximab) • 1 SRMA (Owattanapanich et al 2018) of 2 cohort studies (Hie et al 2014, Jestin et al 2017) (n=163) showed a statistically significant lower risk of relapse (defined as a recurrence of an acute episode of TTP after remission) in people receiving rituximab prophylaxis (median follow-up 3 years) (OR 0.09 (95% CI 0.04 to 0.24), p<0.00001). **(VERY LOW)** • 1 cohort study (Hie et al 2014) (n=48) found lower rates of relapse over the study period with pre-emptive rituximab (3/30 (10%) than with no pre-emptive rituximab (historical controls 7/18 (38.9%)) (p value not reported) **(VERY LOW)** (these data are included in the SRMA (Owattanapanich et al 2018) pooled estimate of relapse rate). Hie et al (2014) reported a statistically significant lower rate of acute TTP episodes per year (0, IQR 0 to 0.81, median follow-up 36 months) with pre-emptive rituximab than with no pre-emptive rituximab (0.5, IQR 0.12 to 0.5, from historical controls, median follow-up 60 months); p<0.01. **(VERY LOW)** Relapse-free survival in this study (from the first rituximab infusion for pre-emptive rituximab group; from first regular assessment of ADAMTS13 activity after an acute episode for no pre-emptive rituximab group) was not reached in the pre-emptive rituximab group (median follow-up 36 months) and was 9.3 years in the no pre-emptive rituximab group (median follow-up 60 months), p=0.049. **(VERY LOW)** • 1 case series with an additional comparison to an historical group (Jestin et al 2017) (n=115) found lower rates of relapse (reappearance of neurological manifestations, renal failure and/or thrombocytopenia with no other identifiable cause after durable remission) over the study period in those given pre-emptive rituximab (14/92 (15%)) than those not given pre-emptive rituximab (historical controls 17/23 (74%)) (p value not reported), **(VERY LOW)** (these data are included in the SRMA (Owattanapanich et al 2018) pooled estimate of relapse rate). Jestin et al (2017) reported that the median cumulative incidence of relapse was lower with pre-emptive rituximab (0 episodes per year, IQR 0 to 1.32) than with no pre-emptive rituximab (0.26 episodes per year, IQR 0.19-0.46); p<0.001. **(VERY LOW)** Jestin et al (2017) also compared data for the pre-emptive rituximab group from a period before pre-emptive rituximab

Certainty of evidence: Very low	(assumed the same population, median follow-up 54 (IQR, 45 to 82) months) and found 0.33 episodes per year (IQR 0.23 to 0.66), p<0.001 compared to after pre-emptive rituximab**.** The median number of iTTP episodes in the pre-emptive rituximab group (time period not reported, presumed to be over the whole follow-up period of 35.8 (IQR 23.3 to 68) months) was 0 (IQR 0 to 4). This was not reported for the no pre-emptive rituximab historical control group but was compared to a period before pre-emptive rituximab treatment (assumed the same population median follow-up 54 (IQR, 45 to 82) months) and reported that the median number of iTTP relapse episodes prior to pre-emptive rituximab was 3 (IQR 2 to 3), p<0.01 compared to after pre-emptive rituximab. **(VERY LOW)** There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study but the numbers are unclear **These studies provided very low certainty evidence that compared to no rituximab treatment, prophylactic rituximab substantially reduces the rate of relapse at up to 38 months follow-up. For example, in the meta-analysis of the only two comparative studies that were identified, the OR for relapse (recurrence of an acute episode of TTP) was 0.09 (95% CI 0.04 to 0.24), p<0.00001 (median follow up 3 years).**
	Treatment In total 6 studies (1 SRMA of 6 cohort studies, 4 cohort studies and 1 case series) provided evidence relating to relapse rate measured at different timepoints. 1 study assessed relapse rate in people with idiopathic TTP and either no response or a disease exacerbation during intensive TPE, 1 study was in relapsed or refractory TTP, and 3 studies were in acute de novo or relapsed TTP. The SRMA did not specify the type of TTP. • 1 SRMA (Owattanapanich et al 2019) of 6 cohort studies (n=365) with follow-up ranging from 1 year to 4 years showed a statistically significant reduction in relapse rate in people with rituximab treatment compared with conventional treatment (OR 0.40, 95% CI 0.19 to 0.85), p=0.02. **(VERY LOW)** At 1 to 2 years: • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found no difference in the proportion who

	relapsed within 12 months (rituximab 0% vs no rituximab 9.4%, p=0.34). **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (n=124) and 20.6 months follow-up found people with rituximab treatment appeared to be protected from relapse at 1 year (Kaplan-Meier analysis, p=0.01). **(VERY LOW)** • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (n=80) and follow-up of ≥1 year found significantly fewer relapses following rituximab treatment (10%, occurring at median 27 months, range 17 to 31) compared with control (53%, occurring at median of 18 months, range 3 to 60), p=0.0011. **(VERY LOW)** • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) found relapse-free survival at 2 years was significantly higher with rituximab than no rituximab, p=0.02. In multivariate analysis, rituximab use protected against relapse within 2 years: hazard ratio (HR) 0.18 (95% CI 0.04 to 0.80). • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) provided non-comparative evidence for relapse rates in patients previously treated with rituximab (n=14, 18 episodes): 5 relapses occurred in 3 patients during 22 months (range 16 to 53) follow-up. **(VERY LOW)** At median follow-up of approximately 3 years: • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found that at median follow-up of 33 months (SD 17.4) (rituximab) and 35.3 months (SD 28.5) (no rituximab), relapse did not differ between groups (p=0.68). **(VERY LOW)** At median follow-up of approximately 4 years: • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) found no difference in the proportion of acute episodes that relapsed (rituximab 12.3% vs no rituximab 16.4%, p=0.51) during a median follow-up of 3.8 years (IQR 2.4 to 7.3) (rituximab) and 3.9 years (IQR 1.7 to 8.1) (no rituximab). **(VERY LOW)** • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) provided non-comparative evidence for relapse rates in rituximab naïve patients (n=86) (13.4% of patients who achieved remission, median follow-up 45 months (range 4 to 100). **(VERY LOW)**

	At 5 years: • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) found no difference in relapse-free survival at 5 years between those treated with rituximab and no rituximab (Kaplan-Meier analysis, p=0.31). Similarly, multivariate analysis found no significant difference between groups for relapse within 5 years. **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (n=124) and a median of 20.6 months follow-up found that the effect of rituximab reduced with time, with a HR for time interaction of 1.002 (95% CI 1.0007 to 1.003) per day after administration, and a HR of 1.0 at 2.6 years. At 5 years, people with rituximab treatment did not appear to be protected from relapse (Kaplan-Meier analysis, p=0.45). **These studies provided very low certainty evidence that compared to conventional treatment, rituximab reduces relapse rate in people with acute TTP during the first two years after treatment but no evidence that it does so at longer time points.**
Disease response **Certainty of evidence: Very low**	Disease response is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised (for example but not limited to a normalisation of platelet number, normalisation of ADAMTS13 activity, and time to remission). **Prophylaxis** In total three studies (one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported evidence relating to disease response measured at different time points from 15 months to 36 months. Two studies compared results for disease response measures between people treated with rituximab and people not treated with rituximab. However, details of the types of comparator treatments were not described in the comparator studies. At median 15 months follow up (pre-emptive rituximab) • 1 case series (Westwood et al 2017) (n=76 patient episodes) provided non-comparative evidence of complete disease response (ADAMTS13 ≥60%): this occurred in 60/76 (78.9%) patient episodes; partial disease response ADAMTS13 30%-59%) in 10/76 (13.2%) patient episodes; and partial response or complete response (ADAMTS13

	≥30%) occurred in 70/76 (92.1%) patient episodes. **(VERY LOW)** Median time to ADAMTS13 recovery was 1 (range <1 to 5) months. **(VERY LOW)** At median 32-36 months follow up (pre-emptive rituximab) • 1 cohort study (Hie et al 2014) (n=48) found the median ADAMTS13 activity % was 58.5%[1] (IQR, 30.5% to 86.3%) with pre-emptive rituximab but did not report data for the no pre-emptive rituximab group. **(VERY LOW)** Durable ADAMTS13 recovery (median follow-up 36 (IQR 24 to 65) months) (normal ADAMTS13 activity defined by authors as ≥50%) in the pre-emptive rituximab group was reported in 20/30 (66.7%). The remaining 10/30 had persistent/subsequent ADAMTS13 deficiency. Data were not reported for the no pre-emptive rituximab group. **(VERY LOW).** • 1 case series (Jestin et al 2017) (n=92) provided non comparative evidence of sustained ADAMTS13 recovery following a single course of pre-emptive rituximab and considered 34/92 (37%) to be long-term responders (no definition reported) over the period of follow-up (median follow-up 31.5 (IQR 18 to 65) months). **(VERY LOW)** This was not reported for the no pre-emptive rituximab group. Persistent/severe ADAMTS13 deficiency (undetectable ADAMTS13 activity) 6 months after a single course of pre-emptive rituximab was seen in 13/92 (14.1%) **(VERY LOW)** and at least 1 severe recurrence of ADAMTS13 deficiency (<10% activity) following a single course of pre-emptive rituximab in 45/92 (49%) (period of follow-up not reported). **(VERY LOW)** Neither of these outcomes were reported for the no pre-emptive rituximab groups. There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study. **These studies provided very low certainty evidence that patients may have had a disease response to prophylactic rituximab treatment up to 40 months follow- up. For example, one study reported that 34/92 patients (37%) were considered long-term responders (definition not reported) and another study reported that 20/30 (67.7%) patients had durable ADAMTS13 recovery (ADAMTS13 activity ≥50%) at a median follow-up of 36 months. However, no comparative data were reported for patients who were not treated with rituximab.**
Certainty of evidence: Very low	**Treatment** In total 4 studies (3 comparative cohort studies, 1 case series) provided evidence relating to disease response following rituximab treatment at different timepoints. Disease response following no rituximab was not reported. All 3 studies reported time to remission or durable remission, 2

studies reported platelet normalisation, 1 study reported normalisation of ADAMTS13 activity, and 1 study reported normalisation of B-cell numbers. 1 study assessed disease response in people with idiopathic TTP and either no response or a disease exacerbation during intensive TPE, and 2 studies in acute de novo or relapsed TTP.

Time to remission:

- 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (rituximab n=22) found the mean time from rituximab initiation to durable remission (complete response with no further thrombocytopenia or clinical worsening ≥30 days following the first day of platelet count recovery) (days from the first TPE to the beginning of remission): was 12 days (SD 6.7) in 21 patients with durable remission. Data were not reported for the control group. **(VERY LOW)**
- 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (rituximab n=40) reported median time to remission (sustained platelet count > 150 x 10^9/L for 2 consecutive days) was 12 days. Data were not reported for the control group. **(VERY LOW)**
- 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported median time to remission (sustained platelet count > 150 x 10^9/L for 2 consecutive days, unclear if from admission or first infusion) was 14 days (range 4 to 52) in 82 rituximab naïve patients who achieved remission, and 7 days from admission (range 0 to 25) or 8 days from first infusion (range 4 to 25) in previously treated patients (n=14, remission in 16/18 episodes). **(VERY LOW)**

Platelet normalisation

- 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found platelet count recovery (Kaplan-Meier estimates up to 160 days) was shorter in the rituximab group compared to the no rituximab group p 0.03). **(VERY LOW)**
- 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (rituximab n=60) found that for patients receiving rituximab who had not yet achieved a normal platelet count (n not reported), platelet count normalisation occurred a median of 8 days (IQR 5 to 11) after rituximab administration (not stated if this is from

	first or last infusion). Data were not reported for the control group. **(VERY LOW)** Normalisation of ADAMTS13 activity • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found ADAMTS13 activity was higher in the rituximab group than controls at 1 month (p=0.007), 3 months (p=0.01), 6 months (p=0.02) and 9 months (p=0.003). At 12 months there was no significant difference between groups (p=0.12), data in a figure only. **(VERY LOW)** Normalisation of B cell numbers • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (rituximab n=40) reported CD19 levels (a marker of B-cell levels, normal range 5% to 15%). For the group treated with rituximab, levels were 23% (range 2.6% to 39.90%) on admission, 21% (range 10.7% to 51.1%) before the first infusion, 1.4% (range 0% to 2.78%) at first infusion, 0.97% (range 0% to 5.43%) at second infusion, and 0.5% (range 0% to 2.78%) before fourth infusion. The authors reported that "normalisation of B cell numbers occurred in 75% of patients, with levels above the normal range within 12 months (7.76%; range 0.46 to 32.5). However, this was not associated with further relapse." **(VERY LOW)** **These studies provided very low certainty evidence that median time to remission following rituximab treatment ranges from 8 to 14 days. One study found ADAMTS13 activity was higher with rituximab than no treatment up to 9 months after treatment but not at 12 months. One study reported a substantial reduction in B-cell numbers following rituximab treatment.**
Hospitalisation **Certainty of evidence: Not applicable**	Hospitalisation due to an acute TTP episode or as a reaction to rituximab (such as acute or delayed serum sickness/anaphylaxis) is important to patients because it indicates that their condition is not adequately controlled. It can increase morbidity and mortality and impacts quality of life from a physical, and psycho-social perspective in the short term with possible implications for the longer term.
	Prophylaxis **No evidence was identified for this outcome.**
Certainty of evidence: Not applicable	**Treatment** See below under important outcomes.

Important outcomes	
Quality of life **Certainty of evidence:** **Not applicable**	Quality of life is an important outcome to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality of life questionnaires include but are not limited to the EQ-5D & SF 36 which can provide information regarding improvement in symptoms. Disease specific quality of life questionnaires can provide information regarding improvement in symptoms.
	Prophylaxis **No evidence was identified for this outcome.**
Certainty of evidence: **Not applicable**	**Treatment** **No evidence was identified for this outcome.**
Functional **Certainty of evidence:** **Not applicable**	Functional outcome measures are important to patients as they facilitate enablement, independence and active participation. Functional outcomes may be reflected by measures of end organ damage (e.g. neurological, cardiac) but also by physical tasks, and emotional, and psycho-social measures (e.g. PHQ-9).
	Prophylaxis **No evidence was identified for this outcome.**
Certainty of evidence: **Not applicable**	**Treatment** **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:** **Not applicable**	Hospitalisation is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention.
	Prophylaxis See above under critical outcomes. No evidence was identified for this outcome.
Certainty of evidence: **Very low**	**Treatment** In total 3 studies (2 comparative cohort studies and 1 case series) reported length of hospital stay in people with de novo or relapsed acute TTP. It is assumed that this was for the initial admission, but it is not explicitly stated by the papers. • 1 prospective cohort study with historical controls (Scully et al 2011) (n=80) found no difference in the number of days admitted between rituximab treated

	patients (16.5 days, range 5 to 49) and controls (20 days, range 5 to 62), p=not significant. **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (n=124) reported median hospital stay was 18 days (IQR 11 to 27) in the rituximab group and 9 days (IQR 7 to 14) in the no rituximab group (p value not reported). **(VERY LOW)** • 1 case series (Westwood et al 2013) (n=86) reported median hospital stay of 19 days (range 4 to 86) in rituximab naïve patients (n=86) and 10 days (range 4 to 29) in previously treated patients (n=14). **(VERY LOW)** **These studies provided very low certainty evidence, and did not provide evidence of a difference in length of hospital stay for what is assumed to be the acute admission with rituximab treatment compared with no rituximab. Median length of stay ranged from 16.5 days to 19 days with rituximab and 9 days to 20 days with no rituximab.**
Safety	
Safety / Adverse effects **Certainty of evidence: Very low**	Safety / adverse effects are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. It reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. **Prophylaxis** In total three studies (one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported evidence relating to adverse events from pre-emptive rituximab treatment groups. Follow-up differed between these studies from 15 months to 36 months; the time of reporting of these adverse events was not reported. No studies compared results between people treated with pre-emptive rituximab and people not treated with pre-emptive rituximab. • 1 case series (Westwood et al 2017) (n=76 patient episodes) reported adverse event rates for those treated with pre-emptive rituximab by patient episodes. 15/76 (19.7%) patient episodes had infusion reactions, 23/76 (30.3%) patient episodes had any adverse event, 8/76 (10.5%) patient episodes had non infusion reactions and there were no Hepatitis B reactivations, significant episodes of abnormal liver function tests or cases of hypogammaglobulinemia. **(VERY LOW)** • 1 cohort study (Hie et al 2014) (n=48) reported treatment related adverse event rates for those in the pre-

	emptive rituximab group (n=30); no comparative data were reported. 4/30 (13%) of people had rituximab treatment related events, no other details were reported. **(VERY LOW)** • 1 case series with an additional comparison group (Jestin et al 2017) (n=115) reported adverse event rates for those in the pre-emptive rituximab group (n=92) as non-comparative data. 19/92 (20.7%) of people had rituximab treatment related events, no other details were reported except that none of these events led to rituximab interruption, 12/92 (13.0%) had moderate intolerance within 3 days but there were no severe infections, cases of hypogammaglobulinemia, progressive multifocal leukoencephalopathy or Kaposi sarcoma. **(VERY LOW)** There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study. In total three studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group) reported evidence relating to mortality rates on study. All three studies compared results for mortality between people treated with pre-emptive rituximab and people not treated with pre-emptive rituximab; details of the types of comparator treatments were not described in the comparative studies, and the SRMA reports the same data as the two comparative studies. • Three studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group) reported evidence relating to deaths. 1 cohort study (Hie et al 2014) (n=48) reported no deaths in the pre-emptive rituximab group and 2 deaths in the no pre-emptive rituximab group (p value not reported). **(VERY LOW)** The SRMA (Owattanapanich et al 2018) calculated the odds ratio for death in the Hie et al (2014) study as 0.11 (95% CI 0.00 to 2.39). **(VERY LOW)** 1 case series with an additional comparison to an historical group (Jestin et al 2017) (n=115) reported 2/92 (2.17%) deaths in the pre-emptive rituximab group and 2/23 (8.69%) deaths in the no pre-emptive rituximab group (p value not reported). **(VERY LOW)** The SRMA (Owattanapanich et al 2018) calculated the odds ratio for death in the Jestin et al (2017) study as 0.12 (95% CI 0.01 to 1.33); however, this was based on a different value for deaths in the rituximab group as the SRMA reported 1 participant had died; and Jestin et al (2017 reported that 2 had died. **(VERY LOW)** There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study.
Certainty of evidence: Very low	**These studies provided very low certainty non-comparative evidence relating to adverse events, with**

	rates ranging from 13% for rituximab treatment related events in one study to 30% for any adverse event in another study, and very low certainty evidence that there is no difference in mortality rates when comparing rituximab treatment to no-rituximab treatment.
	Treatment In total 4 studies (3 comparative cohort studies and 1 case series) reported safety / adverse events following treatment with rituximab. Adverse events following conventional treatment were not reported by the studies. Up to 1 year follow-up • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (rituximab n=40) reported 1 chest pain during infusion, 5 chest pain following infusion, 2 chest pain not related to rituximab, and 26 infections following infusion (3 of which were related to infusion lines). Neurologic, haematologic, reproductive and other events during admission and up to one year follow-up were also reported, with the following noted as being possibly due to rituximab: 5 joint pain, 3 skin rash, and 2 hair loss/thinning, Median follow-up 3 to 4 years • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (rituximab n=22) reported narratively that no severe adverse events or clinically significant infections occurred. • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (rituximab n=58) reported that rituximab led to respiratory distress in one patient. No other severe adverse events occurred. • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported no documented increase in infections. Mild joint pains (number not reported), chest pain in six cases (unknown if associated with TTP rituximab), no progressive multifocal leukoencephalopathy. **These studies provided very low certainty non-comparative evidence of adverse events following treatment with rituximab, with one patient experiencing respiratory distress and no other severe adverse events reported.**
Abbreviations CI - Confidence Interval; EQ-5D - EuroQol 5 dimensions; HR - Hazard Ratio; IQR - Inter-quartile range; iTTP - idiopathic (immune) thrombotic thrombocytopenic purpura; OR - odds ratio; PHQ-9 - Patient Health Questionnaire-9; SF-36 - Short-	

form 36; SD – Standard Deviation; SRMA - Systematic review and meta-analysis; TPE – therapeutic plasma exchange; TTP - Thrombotic Thrombocytopenic Purpura

In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the cost effectiveness of prophylactic rituximab compared with no rituximab?
AND
In people diagnosed with acute immune TTP, what is the cost effectiveness of rituximab compared with no rituximab?

Outcome	Evidence statement
Cost effectiveness	Cost effectiveness models consider direct and indirect costs, effects, and quality of life.
	Prophylaxis **No evidence was identified for cost effectiveness.**
	Treatment **No evidence was identified for cost effectiveness.**

From the evidence selected, for people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, are there any subgroups of patients that may benefit from prophylactic rituximab more than the wider population of interest?
AND
From the evidence selected, for people diagnosed with acute immune TTP, are there any subgroups of patients that may benefit from rituximab more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**Prophylaxis** **No evidence was identified for patient subgroups.**
Mortality **Certainty of evidence:** **Very low**	**Treatment** **Mortality** 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32). Mortality occurred in 2/54 (3.7%) of the early subgroup and 2/32 (6.3%) of the late subgroup (p value not reported). **(VERY LOW)** **One study provided very low certainty evidence that mortality may be lower following early compared with late administration of rituximab, but no statistical analysis was reported**. **Relapse rate**

Relapse rate **Certainty of evidence:** **Very low**	1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32). There was no difference in relapse free survival between early and late subgroups (p=0.77). **(VERY LOW)** **One study provided very low certainty evidence that relapse free survival is not different following early compared with late administration of rituximab**.
Disease response **Certainty of evidence:** **Very low**	**Disease response** 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32), and administration weekly or every 3 days. • Median time to remission from admission: early rituximab group 12 days (range 4 to 52); late rituximab group 20 days (range 4 to 42), p<0.001. **(VERY LOW)** • Median time to remission from first infusion: early rituximab group 10 days (range 2 to 50); late rituximab group 9 days (range 0 to 30), p=0.67. **(VERY LOW)** • Early rituximab group: median time to remission from admission: rituximab administration every 3 days group 13 days; weekly group 9 days, p=0.07. **(VERY LOW)** • Late rituximab group: median time to remission from admission: rituximab administration every 3 days group 18 days; weekly group 21 days, p=0.48. **(VERY LOW)** • Early rituximab group: median time to remission from infusion: rituximab administration every 3 days group 11 days; weekly group 7 days, p=ns. **(VERY LOW)** • Late rituximab group: median time to remission from infusion: rituximab administration every 3 days group 8 days; weekly group 9 days, p=ns. **(VERY LOW)** **One study provided very low certainty evidence that time to remission (from the point of admission but not from first infusion) is lower following early compared with late administration of rituximab, but no evidence of a difference was found between administration weekly or every 3 days.**
Hospitalisation **Certainty of evidence:**	**Hospitalisation** 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3

Very low	days from admission, n=54) or late (> 3 days from admission, n=32). Median length of admission: early rituximab group 16 days (range 4 to 86); late rituximab group 23 days (range 7 to 52), p=0.01. **One study provided very low certainty evidence that the median length of admission is lower following early compared with late administration of rituximab**.
Abbreviations NS – not significant; TTP - Thrombotic Thrombocytopaenic Purpura	

From the evidence selected, what are the criteria used by the research studies to define those people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency who are eligible to commence prophylactic treatment?
AND
From the evidence selected, what are the criteria used by the research studies to define those people diagnosed with acute immune TTP who are eligible to commence treatment?

Outcome	Evidence statement
Criteria used by research studies	**Prophylaxis** Three studies (one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported the criteria used to define people with acute immune TTP in clinical remission following immunosuppression and ADAMTS13 deficiency who received prophylactic treatment or not and were eligible for the study. However it is uncertain whether criteria for eligibility for the study were the same as criteria for eligibility to commence treatment (which were not reported) and it is possible that additional participants received prophylactic treatment but did not meet the study criteria. Study eligibility criteria were: • 1 cohort study (Hie et al 2014) (n=48) commenced prophylactic treatment with rituximab in people with idiopathic acquired TTP and severe ADAMTS13 deficiency (< 10%) at remission or after an initial, partial, or complete recovery (11 to 29 months) from a previous acute episode. • 1 case series with an additional comparison group (Jestin et al 2017) (n=115) commenced prophylactic treatment with rituximab in people with idiopathic (immune) TTP, durable remission (not defined) from a previous acute episode and severe ADAMTS13 deficiency (level not defined but persistent following clinical remission or following an initial partial or complete enzyme activity recovery).

- 1 case series (Westwood et al 2017) (n=45) commenced prophylactic treatment with rituximab in people with TTP in remission, at least 1 previous acute TTP episode and at high risk of relapse (low ADAMTS13 levels on routine monitoring). Low ADAMTS13 level was defined as ≤15% except in 2 cases which had levels of 16% and 17% respectively as they were deemed to be at high risk of relapse on their previous episodes and relapse history.

Three studies provide information on the criteria used to define people who received treatment with prophylactic rituximab and were eligible for their study. Criteria varied and were not always fully defined/reported, but included, where reported, severe ADAMTS13 deficiency at remission or after partial or complete recovery after an acute episode of TTP, and ADAMTS13 levels of under 10% or under 15%.

Treatment

Five studies (two prospective cohort studies with historical controls, two retrospective cohort studies and one retrospective case series) reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment.

- 1 prospective cohort study with historical controls (Froissart et al 2012) (n=79) included people with severe, acquired ADAMTS13 deficiency: thrombotic microangiopathy (Coombs negative microangiopathic haemolytic anaemia, acute peripheral thrombocytopenia and absence of an identifiable cause for the thrombocytopenia and microangiopathic haemolytic anaemia); mild renal involvement and ADAMTS13 activity <10%.
- 1 retrospective cohort study (Kubo et al 2020) (n=156) included people with severely deficient ADAMTS13 activity (<10% of normal) and detectable ADAMTS13 inhibitor and either refractory TTP, defined as persistent thrombocytopenia despite five treatments with TPE and corticosteroids, or relapsed TTP defined as thrombocytopenia (<150 × 109/l) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped.
- 1 prospective cohort study with historical controls (Scully et al 2011) (n=80) included adults with de novo or relapsed acute TTP (thrombocytopenia, microangiopathic haemolytic anaemia, normal clotting screen, increased lactate dehydrogenase to 1.5 times normal upper limit).
- 1 retrospective cohort study (Sun et al 2019) (n=124) included people with immune-mediated TTP, thrombocytopenia (<150 x 109 platelets/L), schistocytosis, and one of: ADAMTS13 activity level ≤10% or ADAMTS13 activity level between 10% and 20% with a positive inhibitor titre by

	Bethesda assay and/or detectable anti-ADAMTS13 immunoglobulin G present in plasma. • 1 case series (Westwood et al 2013) (n=86) included people with acute de novo or relapsed TTP (presence of thrombocytopenia, microangiopathic haemolytic anaemia, normal clotting screen, increased lactate dehydrogenase to ≥ 1 x upper limit of normal). **Five studies reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment.**
Abbreviations TPE – therapeutic plasma exchange; TTP - Thrombotic Thrombocytopaenic Purpura	

From the evidence selected, what dose regimens of prophylactic rituximab were used?

Outcome	Evidence statement
Dose regimens	**Prophylaxis** Four studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported the doses of prophylactic rituximab given to participants. 1 cohort study (Hie et al 2014) (n=48) gave pre-emptive rituximab 375 mg/m^2. The number of infusions per course was at the physician's discretion; 11 had 1 infusion; 2 had 2 infusions and 17 had 4 infusions per course (one infusion per week). 1 case series with an additional comparison to an historical group (Jestin et al 2017) (n=115) used either rituximab 375 mg/m^2 (in 79/92 (85.9%)) or 500 mg/m^2 (in 13/92 (14.1%)). The study did not report outcomes by dose subgroup. 1 SRMA reported only the two studies above, with no additional information on doses. 1 case series (Westwood et al 2017) (n=76 patient episodes) reported data by four rituximab dose subgroups (375 mg/m^2 once per week for 4 weeks (standard dose group); 200 mg once per week for 4 weeks (reduced dose group); 500 mg once per week for 4 weeks (intermediate dose group); 100 to 1000 mg rituximab in 1 to 5 doses ('other dose groups)). Westwood et al (2017) reported that standard-dose rituximab was generally used at the beginning of the study but that reduced dose regimens were used over time because of evidence from other autoimmune disorders. The authors also reported that intermediate doses were used more recently in those at risk of hepatitis B reactivation. Results for disease response were reported for the four groups, with different durations of follow-up:

	• Standard dose 375 mg/m^2 once per week for 4 weeks (n=24 patient episodes), median follow up 17.5 (range 1 to 141) months. o Complete response (ADAMTS13 ≥60%)[2]: 18/24 (75%) episodes. o Partial response (ADAMTS13 30% to 59%): 3/24 (12.5%) episodes o Partial response or complete response (ADAMTS13 ≥30%): 21/24 (87.5%) episodes o Time to ADAMTS13 recovery median 1 (range <1 to 5) months • Reduced dose 200 mg once per week for 4 weeks (n=19 patient episodes), median follow up 25 (range 9 to 43) months: o Complete response (ADAMTS13 ≥60%): 16/19 (84.2%) episodes. o Partial response (ADAMTS13 30% to 59%): 2/19 (10.5%) episodes o Partial response or complete response (ADAMTS13 ≥30%): 18/19 (94.7%) episodes o Time to ADAMTS13 recovery median 1 (range <1 to 4) months • Intermediate dose 500 mg once per week for 4 weeks (n=17 episodes), median follow up 10 (range 3 to 20) months: o Complete response (ADAMTS13 ≥60%): 12/17 (70.6%) episodes. o Partial response (ADAMTS13 30% to 59%): 4/17 (23.5%) episodes o Partial response or complete response (ADAMTS13 ≥30%): 16/17 (94.1%) episodes o Time to ADAMTS13 recovery median 1 (range <1 to 3) months • Other doses 100 to 1000 mg (n=16 episodes), median follow up 21 (range 3 to 112) months: o Complete response (ADAMTS13 ≥60%): 14/16 (87.5%) episodes. o Partial response (ADAMTS13 30% to 59%): 1/16 (6.25%) episodes o Partial response or complete response (ADAMTS13 ≥30%): 15/16 (93.4%) episodes o Time to ADAMTS13 recovery median 1 (range <1 to 4) months Subgroup analyses were undertaken by Westwood et al (2017). There was no statistically significant difference in complete response between standard-dose versus reduced-dose versus intermediate-dose (p=0.61), and no statistically significant differences in time to ADAMTS13 recovery between standard-dose versus reduced-dose versus intermediate-dose (p=0.69). No other statistical comparisons were reported.

	Four included studies provide information on the doses of rituximab used prophylactically to prevent acute TTP. The doses used varied widely between patients, but the most common dose was 375 mg/m^2, usually once a week for four weeks. One included study, however, reported that lower dose rituximab regimens were used over time in their study based on evidence of its use from other autoimmune disorders.
	Treatment Not applicable
Abbreviations SRMA - Systematic review and meta-analysis	

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** patients can have severe problems in walking about and other disabilities, especially if they have suffered a stroke or seizures.
- **ability to provide self-care:** patients can have moderate-severe problems in washing or dressing and cooking as well as attending hospital and doctors' appointments on their own.
- **undertaking usual activities:** patients can have severe problems in doing their usual activities, including going to work or making a living. Fatigue, memory loss, concentration problems and aphasia and symptoms of PTSD can make returning to their 'old life' challenging and often impossible.
- **experience of pain/discomfort:** patients can have moderate pain or discomfort, particularly in joints. Patients are frequently diagnosed with fibromyalgia.
- **experience of anxiety/depression:** patients can be severely - extremely anxious or depressed. PTSD can be a feature among patients due to the sudden and unexpected onset of TTP and the seriousness of the condition.

Further details of impact upon patients:

Following an episode of acute TTP, patients are often left with long-lasting sequelae. These include life changing fatigue as well as memory and concentration difficulties and seizures. All patients have some degree of global brain injury and are often unable to return to full time work. Similarly, adolescent patients can face difficulty with schooling.

Many people suffer with anxiety as a result of the after-effects of an acute episode of TTP as well as the anxiety of further relapse. Additionally, patients can suffer recurrent transient ischaemic attacks and fits following acute TTP. This can result in patients being unable to drive which can massively impact their independence. Some patients experience extreme anxiety and depression when their ADAMTS13 levels become low.

Further details of impact upon carers:

TTP can lead to a high burden on the carer to help with many self-care tasks, which may be difficult or impossible for the person during an acute relapse. Families and/or carers may have to help with tasks such as bathing, cleaning teeth, dressing and undressing, cooking and preparing meals, ironing, cleaning the house, getting out and about or help using mobility aids. There is a significant burden of anxiety and depression from the carer point of view as well as substantial concern regarding family planning. Additionally, TTP places a significant financial burden on the family of those affected due to the patient themselves being often unable to work as well as a high dependency on carer support. The impact on carers due to the fear of relapse (by both patient and carer) should not be underestimated.

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
The policy proposition supports the off-label use of rituximab as a treatment option in acute TTP and as elective therapy to prevent relapse of TTP. The proposed policy includes children aged 2 years and above, and adults. Rituximab is excluded from tariff. Rituximab has been historically commissioned by Clinical Commissioning Groups in the treatment of TTP so this policy will support equity in access now that the service is commissioned by NHS England.

Considerations from review by National Programme of Care
1) The proposal has received the full support of the Blood and Infection PoC 24th May 2022.