Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	F06X02		
Policy Title	Rituximab for cytopaenia complicating primary immunodeficiency		
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Section K - Activity Impact			
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)	
K1 Current Patient Population & Demography / Growth	K 1.1 What is the prevalence of the disease/condition?	K1. 1 The policy proposes to **routinely commission** the use of rituximab for autoimmune cytopaenia as a complication of primary immune deficiency (PID). Epidemiological data on PID are limited and it is thought that this is under-diagnosed and under-reported.[i] There were 2,222 patients on the UK PID registry in 2012[ii]. Using ONS population estimates suggests that this could be c. 1,890 for England in 2014/15.[iii] The prevalence of **autoimmune cytopaenia** as a complication of those with PID is estimated at c. 175 in England in 2014/15.[iv]	

	K1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	K1.2 Only a subset of the population identified in K1.1 could be eligible for rituximab. It is estimated that **10 to 40** patients may be eligible for rituximab under the policy;[v] however there is much uncertainty surrounding these figures.[vi] Of these patients, it is estimated that[vii]: • ~ 10 to 20 currently receive rituximab; and • ~ 0 to 20 additional patients would be eligible to receive it under the policy.
	K1.3 What age group is the treatment indicated for?	K1.3 The policy indicates this treatment for use in adults and children.[viii]
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 Based on the UK PID (primary immunodeficiency) registry, 22% of patients registered are aged 16 or under, and overall c. 48% are female and 52% are male.[ix]
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 As mentioned in K1.2, it is estimated that 10 to 20 patients currently receive rituximab for this indication and this would be taken alongside the maintenance dose of intravenous immunoglobulin (IVIg). [x] All eligible patients will have tried, but not responded adequately to, high doses of IVIg and steroids[xi]: • The 10 to 20 patients who are estimated to currently receive rituximab would **also** be maintained on a dose of 0.4 – 0.6g/kg of IVIg administered every 2 to 4 weeks; and • For the 0 to 20 additional patients under the policy it is estimated

		that[xii]: • c. 25% are likely to exhibit a response to high dose IVIg, and as such would be maintained on a high dose of 1-2g/kg of IVIg administered every 2 to 4 weeks[xiii]; and • c. 75% who fail to respond to high dose IVIg, would revert back to the maintenance dose of 0.4-0.6g/kg of IVIg administered every 2 to 4 weeks, and other treatment options would be explored. [xiv]
	K1.6 What is the projected growth of the disease/condition prevalence (prior to applying the new policy) in 2, 5, and 10 years?	K1.6 No disease-specific growth rate has been identified for cytopaenia complicating primary immunodeficiency in this review. The **prevalent** population is estimated to grow in line with demographic growth; as such the future prevalent population could be in the region of:[xv] • ~ 1,920 in 2016/17 (year 1) • ~ 1,935 in 2017/18 (year 2) • ~ 1,975 in 2020/21 (year 5)
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years	K1.7 Activity under the do nothing scenario refers to current activity, assumed to be 'steady state' in future years (as set out in K1.5). Therefore between c. 10 and 20 patients are expected to receive rituximab in future years. [xvi]
	K1.8 How is the population currently distributed geographically?	K1.8 Based on data from the UK PID registry on the geographical distribution of patients enrolled in the UK by city of documenting centre, London has the greatest number of enrolled patients.[xvii]
K2 Future Patient Population &	K2.1 Does the new policy: move to a	K2.1 The policy proposes to add an additional treatment for patients

Demography	non-routine commissioning position / substitute a currently routinely commissioned treatment / expand or restrict an existing treatment threshold / add an additional line / stage of treatment / other?	with autoimmune cytopaenia who are inadequately controlled with high doses of IVIg and steroids.
	K2.2 Please describe any factors likely to affect growth in the patient population for this intervention (e.g. increased disease prevalence, increased survival)	K2.2 No disease-specific growth rate has been identified within this review.
	K 2.3 Are there likely to be changes in geography/demography of the patient population and would this impact on activity/outcomes? If yes, provide details	K2.3 No evidence of changes have been identified in this review.
	K2.4 What is the resulting expected net increase or decrease in the number of patients who will access the treatment per year in year 2, 5 and 10?	K2.4 As stated in K1.2, the number of eligible patients is estimated to be between 10 and 40, with 10 to 20 currently receiving rituximab alongside the maintenance dose of IVIg. As such, the **net increase** in the number of patients receiving rituximab under policy could be between **0 and 20 patients**. These additional patients who would now receive rituximab alongside the maintenance dose of IVIg under the policy, where previously it is estimated that[xviii]: • c. 25% would have been maintained on high dose IVIg; and • c. 75% would have received the maintenance dose of IVIg and be considering other treatment options.

		Therefore although the number of patients receiving rituximab would increase, there would be a decrease in the usage of IVIg for those who would have received the high dose in the 'do nothing'.[xix] It is estimated that c. 74-85% of patients who receive rituximab would respond to it.[xx] Where a patient responds, they would continue to receive rituximab provided that they continue to respond and continue to require treatment.[xxi] Where patients do not respond, they could receive the maintenance dose of IVIg and further treatment options would be considered.[xxii]
K3 Activity	K3.1 What is the current annual activity for the target population covered under the new policy? Please provide details in accompanying excel sheet	K3.1 The current activity has been set out in K1.5.
	K3.2 What will be the new activity should the new / revised policy be implemented in the target population? Please provide details in accompanying excel sheet	K3.2 Based on the current activity identified in K1.5 and the net increase in patients from K2.4, activity in year 1 (2016/17) is estimated to be in the region of **10 to 40**. The lower estimate assumes that: • 10 patients are currently receiving rituximab; and • 0 additional patients would be eligible under the policy. The upper estimate assumes that: • 20 patients are currently receiving rituximab; and • 20 additional patients would be eligible under the policy. As noted in K2.4, for c.25% of additional patients who would receive rituximab there would be a decrease in the usage of IVIg.
	K3.3 What will be the comparative	K3.3 Under the do nothing scenario, the current level of activity is

	activity for the ‘Next Best Alternative’ or 'Do Nothing' comparator if policy is not adopted? Please details in accompanying excel sheet	taken to represent the ‘steady state’, which is rolled forward in future years (as set out in K1.7).
K4 Existing Patient Pathway	K4.1 If there is a relevant currently routinely commissioned treatment, what is the current patient pathway? Describe or include a figure to outline associated activity	K4.1 Autoimmune cytopaenias are diagnosed with blood tests measuring levels of platelets and haemoglobin, sometimes a bone marrow sample needs to be obtained to determine whether there is a problem with production of blood cells. First line treatment is focused on steroids and higher doses of intravenous immunoglobulin (IVIG). Some patients with mild autoimmune cytopaenias may require little to no treatment. All patients are regularly monitored, measuring platelet count (patients with ITP) and haemoglobin (patients with AIHA). Approximately 30% of patients develop complications or do not respond to first line treatment. If this happens, the dose of IVIG is increased, and second line treatment options are considered including immune suppression with conventional immunosuppressants or corticosteroids. If these treatments do not work, further treatment options include other anti CD20 agents, splenectomy or cytotoxic immunosuppressive agents, which are non-selective in their mechanism of action and can be associated with considerable toxicity. For ITP, further treatment options include romiplostim and eltrombopag.
	K4.2. What are the current treatment access criteria?	K4.2 Patient who have failed to respond to, or are contraindicated for, standard first and second line therapies.

	K4.3 What are the current treatment stopping points?	K4.3 If the patient responds to first line therapies and their condition is under control and monitored. If splenectomy becomes the more beneficial treatment option for the patient.
K5 Comparator (next best alternative treatment) Patient Pathway	K5.1 If there is a 'next best' alternative routinely commissioned treatment what is the current patient pathway? Describe or include a figure to outline associated activity. K5.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	K5.1 Next best treatments for patients who have failed or are unable to have second line treatments due to contraindications, is a splenectomy. K5.2 Same stopping points as K4.3
K6 New Patient Pathway	K6.1 Describe or include a figure to outline associated activity with the patient pathway for the proposed new policy	K6.1 Failure to respond to first line treatments will lead to consideration of rituximab. Of patients with autoimmune cytopaenia, less than 10% of patients are treated with rituximab. The decision around dosage will need to be taken locally by the clinician treating the patient as part of a MDT. Rituximab is normally administered on a day case basis. If this

		treatment is successful, the dose of IVIG is reduced back to the usual maintenance dose. The patient's condition is monitored by regular blood tests. If treatment with rituximab does not work, further treatment options include other anti CD20 agents, splenectomy or cytotoxic immunosuppressive agents, which are non-selective in their mechanism of action and can be associated with considerable toxicity. For ITP, further treatment options include romiplostim and eltrombopag.
	K6.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	K6.2 Same stopping points as K4.3
K7 Treatment Setting	K7.1 How is this treatment delivered to the patient? o Acute Trust: Inpatient/Daycase/ Outpatient o Mental Health Provider: Inpatient /Outpatient o Community setting o Homecare delivery	K7.1 Rituximab is delivered in a day case setting.[xxiii]

	K7.2 Is there likely to be a change in delivery setting or capacity requirements, if so what? *e.g. service capacity*	K7.2 No change in delivery expected.
K8 Coding	K8.1 In which datasets (e.g. SUS/central data collections etc.) will activity related to the new patient pathway be recorded?	K8.1 Rituximab is a high cost drug excluded from tariff, so it should be captured in the high cost drug dataset for routine commissioning.[xxiv] Delivery in a day case setting would be recorded in the SUS data set.
	K8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	K8.2 Activity should be identified through the high cost drug dataset, by drug name and indication. A standard naming convention is recommended.
K9 Monitoring	K9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule?	K9.1 No new or revised requirements identified.
	K9.2 If this treatment is a drug, what pharmacy monitoring is required?	K9.2 Clinicians would be required to record outcomes for those patients treated with Rituximab for autoimmune cytopaenia. (Data on these patients should be submitted to the UKPIN registry including follow-up data and time to relapse after each rituximab dose.)
	K9.3 What analytical information /monitoring/ reporting is required?	K9.3 All centres are expected to participate in national registry data collection, training, examination, peer inspection and guideline development for UKPIN and research into PID as an orphan disease. Data on patients should be submitted to the UKPIN registry including follow-up data and time to relapse after each rituximab dose.

	K9.4 What contract monitoring is required by supplier managers? What changes need to be in place?	K9.4 Contract monitoring is managed by the Commissioning Support Unit (CSU) and the necessary information is then shared with the supplier managers (commissioners).
	K9.5 Is there inked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring?	K9.5 No.
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.6 N/A
	K9.7 Do you anticipate using Blueteq or other equivalent system to guide access to treatment? If so, please outline. *See also linked question in M1 below*	K9.7 Use not expected.
Section L - Service Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
L1 Service Organisation	L1.1 How is this service currently organised? (i.e. tertiary centres, networked provision)	L1.1 Treatment takes place in a specialist centre.

	L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.2 No change expected.
L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 Patients are already on the autoimmune cytopaenia pathway, treatment is overseen by a specialist such as a clinical immunologist, haematologist or oncologist.
	L2.2 Will the new policy change / restrict / expand the sources of referral?	L2.2 No change expected.
	L2.3 Is the new policy likely to improve equity of access	L2.3 No change expected.
	L2.4 Is the new policy likely to improve equality of access / outcomes?	L2.4 Yes, will be commissioned across NHS England so equality of access will improve compared to patients receiving rituximab for other indications.
L3 Implementation	L3.1 Is there a lead in time required prior to implementation and if so when could implementation be achieved if the policy is agreed?	L3.1 No lead in time expected.
	L3.2 Is there a change in provider physical infrastructure required?	L3.2 No change expected.

	L3.3 Is there a change in provider staffing required?	L3.3 No change expected.
	L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	L3.4 No change expected.
	L3.5 Are there changes in the support services that need to be in place?	L3.5 No change expected.
	L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	L3.6 No change expected.
	L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	L3.7 No change expected.
	L3.8 How will the revised provision be secured by NHS England as the responsible commissioner? (e.g. publication and notification of new policy, competitive selection process to secure revised provider configuration)	L3.8 Publication and notification of new policy.

L4 Collaborative Commissioning	L4.1 Is this service currently subject to or planned for collaborative commissioning arrangements? (e.g. future CCG lead, devolved commissioning arrangements)?	L4.1 No
Section M - Finance Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
M1 Tariff	M1.1 Is this treatment paid under a national prices*, and if so which?	M1.1 No (see M1.2).
	M1.2 Is this treatment excluded from national prices	M1.2 This drug is excluded from national prices as a high cost drug.
	M1.3 Is this covered under a local price arrangements (if so state range), and if so are you confident that the costs are not also attributable to other clinical services?	M1.3 Rituximab would be negotiated under local arrangements. The list price for MabThera is c. £873, or c. £1,048 including VAT, for 500mg/50ml.[xxv] The annual cost per patient (including VAT) is set out in M2.1.
	M1.4 If a new price has been proposed how has this been derived / tested? How will we ensure that associated activity is not additionally / double charged through existing routes	M1.4 Not applicable.
	M1.5 is VAT payable (Y/N) and if so has it been included in the costings?	M1.5 VAT would be recoverable under certain specific conditions[xxvi].

		It is assumed here that VAT would not be recoverable and is therefore included in the calculations in sections M2 and M3.
	M1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	M1.6 Not applicable.
M2 Average Cost per Patient	M2.1 What is the revenue cost per patient in year 1?	M2.1 Under the policy, all eligible patients would receive rituximab alongside a maintenance dose of IVIg[xxvii]. As noted in K2.4, It is estimated that in 74-85% of cases patients respond to rituximab and will continue to receive rituximab when relapses occur.[xxviii] Patients who do not respond to rituximab receive one course of rituximab, after which they are no longer treated with rituximab.[xxix] The **cost per patient** in year 1 is estimated to be **c. £40.4k - £93.8k**. These figures include: a) The cost of **IVIg,** estimated at **£34.9k to £88.3k.** This is made up of: • 0.4g/kg of IVIg administered every 4 weeks for the low maintenance dose[xxx] • 0.6g/kg of IVIg administered every 2 weeks for the high maintenance dose[xxxi] • A price for IVIg of £42.5 per gram (excl. VAT)[xxxii] • An administration cost of IVIg of c. £1.3k per day case[xxxiii]. *For reference, where patients receive the high dose of IVIg, defined as 1-2g/kg of IVIg taken once every 2 to 4 weeks, the annual cost per patient could be in the region of **c. £62.7k to £218.2k.*** b) The cost per course of **rituximab** is estimated at c. **£5.5k**.

		This is made up of: • A dose of 2g of rituximab administered over a 2-week period, including 20% VAT, this would be c. **£4.2k.** • The cost of administering the drug is estimated at c. £660 per day case; with two day case visits required per course administration costs are c. **£1.3k.**[xxxiv] Patients who do not respond to rituximab c. 20% of the target population receive a single course of rituximab, at a cost of **c. £5.5k.**
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 Patients who do not respond to rituximab will require further treatment options, as described in K2.4.[xxxv] In addition, they may continue to receive a maintenance dose of IVIg. The cost per person per year for patients who respond to rituximab would comprise both the maintenance dose of IVIg and future costs of rituximab. The mean duration to relapse for patients who respond to rituximab (c. 80% of the target population) has been estimated at 31 months.[xxxvi] Therefore the c. 80% of patients who respond to rituximab may undergo an average of 0.4 courses of rituximab per year, at a cost of **c. £2.3k.**
M3 Overall Cost Impact of this Policy to NHS England	M3.1 Indicate whether this is cost saving, neutral, or cost pressure to NHS England	M3.1 It is expected that NHS England only funds the direct drug costs, and that administration costs are borne by CCGs.[xxxvii] Based on the activity impacts from K2.4, this policy could range from being cost neutral, if no additional patients receive rituximab, to a cost saving where additional patients receive rituximab. For a central scenario (see M6.1 for definition), the policy would be broadly **cost saving** in the region of:

		• c. £0.14m (range: £0 to £0.53m) in 2016/17 • c. £0.18m (range: £0 to £0.62m) in 2017/18 • c. £0.18m (range: £0 to £0.63m) in 2020/21 The range in cost saving is driven by the dosage and frequency of IVIg for those who under the policy would receive rituximab and the maintenance dose of IVIg. This comprises two components: 1) **An increase** in the costs of rituximab for new patients; and 2) **A decrease** in the costs of IVIg for patients who would have been maintained on high dose IVIg if rituximab was not available. The increased costs from rituximab are estimated at • c. £65k (range: £0 to £130k) in 2016/17 • c. £23k (range: £0 to £46k) in 2017/18 • c. £24k (range: £0 to £47k) in 2020/21 The cost savings associated with the reduced use of IVIg are estimated to be in the region of: • c. £0.20m (range: £0 to £0.66m) in 2016/17 • c. £0.20m (range: £0 to £0.66m) in 2017/18 • c. £0.21m (range: £0 to £0.68m) in 2020/21 There could also be further savings if the use of rituximab reduces the requirement of further treatments, as described in K4.1; however these have not been quantified.

	M3.2 Where this has not been identified, set out the reasons why this cannot be measured	M3.2 Not applicable.
M4 Overall cost impact of this policy to the NHS as a whole	M4.1 Indicate whether this is cost saving, neutral, or cost saving for other parts of the NHS (e.g. providers, CCGs)	M4.1 As described in M3.1, it is expected that the administration costs of the drugs would be borne by CCGs. There would be no expected change in IVIg administration frequency, but depending on the net increase in patients receiving rituximab under the policy, this could range from being **cost neutral** to **a cost pressure** in the region of**:** • c. £20.4k (range: £0 to £40.9k) in 2016/17 • c. £7.3k (range: £0 to £14.6k) in 2017/18 • c. £7.3k (range: £0 to £14.9k) in 2020/21
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole	M4.2 Depending on the activity increase under the policy, the cost impact to the NHS as a whole could range from being **cost neutral** to **cost saving** in the region of: • c. £0.11m (range: £0 to £0.49m) in 2016/17 • c. £0.17m (range: £0 to £0.60m) in 2017/18 • c. £0.17m (range: £0 to £0.62m) in 2020/21
	M4.3 Where this has not been identified, set out the reasons why this cannot be measured	M4.3 Not applicable.
	M4.4 Are there likely to be any costs or savings for non NHS commissioners /	M4.4 None expected.

	public sector funders?	
M5 Funding	M5.1 Where a cost pressure is indicated, state known source of funds for investment, where identified *e.g. decommissioning less clinically or cost-effective services*	M5.1 Not applicable.
M6 Financial Risks Associated with Implementing this Policy	M6.1 What are the material financial risks to implementing this policy?	M6.1 The key financial risk relates to the number of additional patients who would receive rituximab as a result of the policy. This has been explained in K1.2, K2.4 and M3.1.
	M6.2 Can these be mitigated, if so how?	M6.2 No mitigations have been identified.
	M6.3 What scenarios (differential assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	M6.3 The **low estimate** of 'cost neutral' assumes that no additional patients receive rituximab under the policy. The **central estimate** assumes: • 10 additional patients receive rituximab under the policy; • 25% of these would previously receive high dose of IVIg[xxxviii], who under the policy receive the maintenance dose of IVIg plus rituximab. • 75% of these patients who previously would have received the maintenance dose of IVIg and were being considered for other treatment options would receive rituximab and the maintenance dose of IVIg under the policy.

		The **upper cost** estimate assumes: • 20 additional patients receive rituximab under the policy; • 25% of these patients would previously have received high dose IVIg[xxxix], who under the policy receive the maintenance dose of IVIg plus rituximab. • 75% of these patients who previously would have received the maintenance dose of IVIg and were being considered for other treatment options would receive rituximab and the maintenance dose of IVIg under the policy.
M7 Value for Money	M7.1 What evidence is available that the treatment is cost effective? *e.g. NICE appraisal, clinical trials or peer reviewed literature* M7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of evidence*	M7.1 No studies were identified in clinical evidence review which considered cost effectiveness M7.2 The assessment used peer reviewed and published evidence.
M8 Cost Profile	M8.1 Are there non-recurrent capital or revenue costs associated with this policy? *e.g. Transitional costs, periodical costs* M8.2 If so, confirm the source of funds to meet these costs	M8.1 None identified. M8.2 Not applicable.

i J D M Edgar et al. (2014). ”The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012”, Clin Exp Immunol. 2014 Jan; 175(1): 68–78. [Available online] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898556/, last accessed: 13/01/2016.

ii J D M Edgar et al. (2014). ”The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012”, Clin Exp Immunol. 2014 Jan; 175(1): 68–78. [Available online] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898556/, last accessed: 13/01/2016.

iii This uses ONS population growth data to estimate 2014/15 figures based on the UKPID figure for 2012; and ONS data on the proportion of the population of England as a share of the UK population.

iv This uses the UKPID register figure of 810 patients with common variable immunodeficiency (CVID); uses ONS population growth data to estimate the 2014/15 figure and to adjust it for England. Based on the policy proposition, approx. 25% of patients with CVID have autoimmune cytopenia.

v According to the policy proposition, currently less than 10% of patients with autoimmune cytopenia are treated with rituximab. Based on discussions with policy working group, the number of patients currently receiving rituximab may lie within the range of 10-20; and the number of eligible patients under the policy would not exceed 40.

vi Based on discussions with policy working group.

vii Based on discussions with policy working group.

viii Policy Proposition.

ix J D M Edgar et al. (2014). ”The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012”, Clin Exp Immunol. 2014 Jan; 175(1): 68–78. [Available online] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898556/, last accessed: 13/01/2016.

x Based on discussions with the policy working group.

xi Based on discussions with the policy working group and on the Policy Proposition.

xii Based on estimates from the policy working group.

xiii Based on discussions with the policy working group and on the Policy Proposition.

xiv Such as other anti-CD20 agents, splenectomy or cytotoxic immunosuppressive agents, and for ITP these could include romiplostim and eltrombopag. Source: Policy proposition.

xv The future figures were calculated based on the prevalence figures set out in K1.1 and assuming that growth is in line with population estimates, based on ONS population projections for the years 2014/15 to 2020/21. Figures are rounded.

xvi Note that the activity is estimated to remain constant due to the low base of patients to which the low population growth rate is applied.

[xvii] J D M Edgar et al. (2014). ”The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012”, Clin Exp Immunol. 2014 Jan; 175(1): 68–78. [Available online] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898556/, last accessed: 13/01/2016.

[xviii] Based on discussions with the policy working group.

xix Based on discussions with the policy working group,

xx Policy proposition.

xxi Policy proposition.

xxii Such as other anti-CD20 agents, splenectomy or cytotoxic immunosuppressive agents, and for ITP these could include romiplostim and eltrombopag. Source: Policy proposition.

xxiii Policy proposition.

xxiv See K9.

xxv Dictionary of medicine, entry for MabThera is £873.15 for 500mg/50ml [Online] http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=7697211000001103&toc=nofloat [Accessed: 13/11/2015]

xxvi Please refer to Section 3.2 of VAT Notice 701/557 (https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products/vat-notice-70157-health-professionals-and-pharmaceutical-products)

xxvii Based on discussions with the policy working group.

xxviii See Gobert et al, 2011, accessed via: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428031/, last accessed: 12/02/2016

xxix Based on discussions with the policy working group.

[xxx] Based on discussions with the policy working group.

[xxxi] Based on discussions with the policy working group.

[xxxii] Dictionary of Medicine, one possible price could be http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=19805211000001108&toc=nofloat, last accessed: 01/02/2016. Note: as IVIg is a blood-derived product, VAT would not be added.

[xxxiii] Based on National Reference Costs 2013/14 HRG code XD34Z: Immunoglobulins Band 1. An MFF uplift of 10% is applied, and this is then uplifted to 2015/16 prices using the inflation and efficiency uplift of c.-1.5% and c -1.6% for 2014/15 and 2015/16 respectively.

[xxxiv] Based on National Reference Costs 2013/14 HRG code XD19Z: Monoclonal Antibodies Band 1. An MFF uplift of 10% is applied, and this is then uplifted to 2015/16 prices using the inflation and efficiency uplift of c.-1.5% and c -1.6% for 2014/15 and 2015/16 respectively.

[xxxv] Such as other anti-CD20 agents, splenectomy or cytotoxic immunosuppressive agents, and for ITP these could include romiplostim and eltrombopag. Source: Policy proposition.

[xxxvi] See Gobert et al, 2011, accessed via: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428031/, last accessed: 12/02/2016, cited in the Policy Proposition.

[xxxvii] Based on discussions with the NHS England Finance Lead.

[xxxviii] The range of annual cost of high dose IVIg, defined as 1-2g/kg of IVIg taken once every 2 to 4 weeks, could be in the region of c. £62.7k to £218.2k. The mid estimate assumes 1.5g/kg of IVIg taken once every 3 weeks, at a cost of c. £140.5k.

[xxxix] The range of annual cost of high dose IVIg, defined as 1-2g/kg of IVIg taken once every 2 to 4 weeks, could be in the region of c. £62.7k to £218.2k. The upper bound is used in this scenario.