DRAFT FOR PUBLIC CONSULTATION

Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	A12X05		
Policy Title	Rituximab for Immunobullous Disease		
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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 This policy proposes to **routinely commission** the use of rituximab for patients with the immunobullous disorders pemphigoid and pemphigus, whose condition is inadequately controlled by steroid therapy and earlier lines of immunosuppressive treatment. The policy proposes **not to routinely commission** the use of rituximab in those with epidermolysis bullosa acquisita (EBA). The prevalence of immunobullous conditions in England in 2014/15 is estimated to be as follows: • c. 5,700 for **pemphigus** (105 per million).[i] • c. 11,700 for **pemphigoid** (215 per million).[ii] • c. The number living with **EBA** is unknown.[iii]	

	K1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	K.1.2 Most patients with immunobulous disease requiring treatment respond to earlier lines of treatment as set out in the policy proposition with immunosuppressive therapies and steroids. The number of patients failing these lines of treatment and therefore **eligible for rituximab** is estimated at **200** in England in 2014/15 – this relates to approximately 1% of the prevalent population.[iv]
	K1.3 What age group is the treatment indicated for?	K1.3 This treatment is indicated for all ages.
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 In one study of incidence in the UK, the median age at presentation was 71 for pemphigus vulgaris and 80 for bullous pemphigoid.[v] However, pemphigus vulgaris may develop at any age.[vi] EBA is a condition that is more common in people over 40.[vii] Based on a study of patients in the UK, the female to male ratio is estimated at 2:1 for pemphigus vulgaris,[viii] and 3:2 for bullous pemphigoid.[ix]
	K1.5 What is the current activity for the target population covered under the new policy?	K1.5 Current activity for the target population is difficult to estimate. Patients that could be suitable for rituximab under the policy would be refractory to initial treatments. These include topical treatments, systemic steroids, and steroid-sparing immunosuppressants or immunosuppressive agents.[x] Under current **routinely commissioned care**, patients at this point in the pathway would be currently considered for IVIg or cyclophosphamide treatment. In 2014/15, it is estimated that up to 40 patients in the target population across England received treatment with intravenous immunoglobulin (**IVIg)**.[xi] Patients who receive IVIg treatment may receive one course per month for three to six months, with an approximate number of four day cases per course.[xii]

		Other patients within the target group may have undergone therapy with **cyclophosphamide** in combination with methylprednisolone. The number of patients is difficult to estimate, but may be under 5% of the target population (under c. 10 patients).[xiii] Due to its toxicity, cyclophosphamide may be generally administered for up to six months, with one day case episode per month to administer cyclophosphamide and two for methylprednisolone; treatment may be repeated after 2 - 4 years if required.[xiv] Some patients may not receive treatment with either IVIg or cyclophosphamide, but may instead be under treatment with high doses of steroids or other **earlier lines of treatment** and achieving inadequate control.[xv] Alternatively, patients may currently be undergoing treatments that are currently **not routinely commissioned**. A total of 7 individual funding requests (IFRs) were submitted for **rituximab** in 2014/15; and 4 in 2015/16 for immunobullous disease.[xvi] Some patients may also be treated with immunoabsorption (in combination with steroids, and often an immunosuppressive agent to prevent rebound) – the treatment is not routinely commissioned for the indications under the policy.
	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 It is estimated that immunobullous diseases would grow at least at the rate of population growth.[xvii] Growing prevalence figures in line with population projections, future prevalence for pemphigus and pemphigoid could be estimated in the region of:[xviii] • ~18,000 persons in 2016/17 • ~18,300 persons in 2017/18 • ~19,200 persons in 2020/21 The number of patients in the target population is estimated to be in the region of 200 to 220 patients in the next five years if ONS demographic

		growth is applied to the target population estimates in K1.2. [xix]
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years	K1.7 Based on K1.5 and using projected population growth, under the 'do nothing' scenario the number of patients on **IVIg** is estimated in the region of: [xx] • ~40 in 2016/17 • ~40 in 2017/18 • ~45 in 2020/21 An the number of patients on **cyclophosphamide** is estimated in the region of:[xxi] • ~ under 10 persons in 2016/17 • ~ under 10 persons in 2017/18 • ~ under 10 persons in 2020/21 The remaining patients in the target population may be on earlier lines of treatment with inadequate control, with few patients on non-routinely commissioned treatments.
	K1.8 How is the population currently distributed geographically?	K1.8 Across England no significant geographical differences in the disease have been identified.
K2 Future Patient Population & Demography	K2.1 Does the new policy: move to a 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?	K2.1 This policy proposes to routinely commission the use of rituximab in refractory pemphigus and pemphigoid, and to not routinely commission its use for EBA. Rituximab would be used as a third line treatment for pemphigus, and as a fourth line treatment for pemphigoid.[xxii]
	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 Increased life expectancy for patients with pemphigus and pemphigoid, for example as a result of rituximab, may also increase the number of patients living with pemphigus and pemphigoid. However this increase could not be quantified.[xxiii]

	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 K2.4 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?	K2.3 None K2.4 Under the policy, the number of patients who would access rituximab treatment in year one is estimated at around c.100, assuming 90% of the target population (i.e. known patients with refractory pemphigoid or pemphigus) receives rituximab and that the policy will be introduced with 50% part year effect in 2016/17.[xxiv] This implies a net increase as compared to the 'do nothing' case (in which rituximab is not commissioned for specified immunobullous diseases). The **total number of patients on rituximab each year** could grow in line with population growth to be approximately (this is not year on year growth):[xxv] • c. 90 in 2016/17 (year 1, 50% PYE) • c. 190 in 2017/18 (year 2, 100% FYE) • c. 200 in 2020/21 (year 5, 100% FYE) Note that these figures represent the increase as compared to the do nothing case, where no patients are receiving rituximab.
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 K3.2 What will be the new activity should the new / revised policy be implemented in the target population? Please provide details in accompanying excel sheet	K3.1 The current activity is set out in K1.5: patients in the target population may currently be using IVIg or cyclophosphamide and a very small number of exceptional cases may be receiving rituximab through the IFR route. K3.2 It is estimated that c. 90% of the target population would successfully take rituximab. After the policy is implemented, it is estimated that c. 5% of patients would continue to receive IVIg (instead of using rituximab), and 2% to 5% would receive cyclophosphamide instead of rituximab.[xxvi] Overall, the activity under the policy is estimated to be in the region of:[xxvii] **Rituximab**

		• c. 90 in 2016/17 (year 1, 50% PYE) • c. 190 in 2017/18 (year 2, 100% FYE) • c. 200 in 2020/21 (year 5, 100% FYE) **IVIg (with each person treated monthly for three to six months)** • c. 25 in 2016/17 (year 1, 50% PYE) • c. 10 in 2017/18 (year 2, 100% FYE) • c. 10 in 2020/21 (year 5, 100% FYE) **Cyclophosphamide (with each person treated once a month for 6 months)** • c. 5 in 2016/17 (year 1, 50% PYE) • c. 5 in 2017/18 (year 2, 100% FYE) • c. 5 in 2020/21 (year 5, 100% FYE) **Steroids and immunosupressants** • c. 80 in 2016/17 (year 1, 50% PYE) • c. under 10 in 2017/18 (year 2, 100% FYE) • c. under 10 in 2020/21 (year 5, 100% FYE)
	K3.3 What will be the comparative activity for the 'Next Best Alternative' or 'Do Nothing' comparator if policy is not adopted? Please provide details in accompanying excel sheet	K.3.3 The 'do nothing' scenario refers to current activity, assumed to be the 'steady state' rolled forward in future years. The future activity levels are therefore set out in K1.7; patients would typically receive IVIg or cyclophosphamide.
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 Once a diagnosis of an immunobullous disorder has been made, generally on the basis of clinical suspicion, characteristic biopsy findings and immunopathology either on serum (indirect immunofluorescence and relevant ELISAs) or on tissue (direct immunofluorescence) treatment should begin. For Pemphigus, first line treatment consists of: - topical treatment, (i.e. wound care, emollients, topical steroid, steroid/antiseptic/anti-inflammatory mouthwash) - systemic steroids (e.g. prednisolone) with steroid sparing immunosupporessant (e.g. azathioprine or mycophenolate).

		For Pemphigoid, initial treatment consists to: - topical treatment - systemic steroid with anti-inflammatory antibiotics.
	K4.2. What are the current treatment access criteria?	K4.2 Access is determined by diagnosis of an immunobullous disorder.
	K4.3 What are the current treatment stopping points?	K4.3 Current treatment stopping points are clinical remission, lack of efficacy or adverse side effects.
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.	K5.1 For Pemphigus: - second line treatment includes topical measures and systematic steroid as with first line, as well as switching to alternate steroid sparing agent (azathioprine or mycophenolate) or mycophenolic acid, - third line treatment includes topical measures and systemic steroid as with first line and additional therapeutic treatment options based on assessment of individual need and consensus of MDT. Options include: cyclophosphamide, intravenous immunoglobulin (IVIG) and immunoadsorption For Pemphigoid: - second line treatment consists of the first line treatment with the addition of steroid sparing immunosuppressant (azathioprine or mycophenolate mofetil) - third line treatment consists of switching to alternate steroid sparing agent (azathioprine or mycophenolate mofetil) or mycophenolic acid - fourth line treatment includes treatment options of cyclophosphamide IV, IVIG and/or immunoadsorption
	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	K5.2 Treatment stopping points are clinical remission, lack of efficacy or adverse side effects.

	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 New Patient Pathway	K6.1 Describe or include a figure to outline associated activity with the patient pathway for the proposed new policy 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.	K6.1 Rituximab would fit in as a third line treatment for pemphigus and fourth line treatment for pemphigoid in the pathway outlined in K4.1 and K5.1. K6.2 In general, it is estimated that of the target population, 90-95% would successfully take rituximab; 5-10% of patients would receive IVIG, cyclophosphamide, or other therapy.[xxviii]
K7 Treatment Setting	K7.1How is this treatment delivered to the patient? ○ Acute Trust: Inpatient/Daycase/Outpatient ○ Mental Health Provider: Inpatient /Outpatient ○ Community setting ○ Homecare delivery K7.2 Is there likely to be a change in delivery setting or capacity requirements, if so what? *e.g. service capacity*	K7.1 Rituximab is delivered in a day case setting.[xxix] K7.2 No change anticipated.

K8 Coding	K8.1 In which datasets (e.g. SUS/central data collections etc.) will activity related to the new patient pathway be recorded? K8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	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.[xxx] Delivery in a day case setting would be recorded in the SUS data set. K.8.2 The activity could be identified using ICD-10 and OPCS codes.[xxxi]
K9 Monitoring	K9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule? K9.2 If this treatment is a drug, what pharmacy monitoring is required? K9.3 What analytical information /monitoring/ reporting is required? K9.4 What contract monitoring is required by supplier managers? What changes need to be in place? K9.5 Is there inked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring? K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.1 No new requirements identified. K9.2 - 9.4 Specialist centres will be required to collaborate as a network for data collection, standards development, the design of audits and participation in national or international trials of new therapies. Such data should be published in the peer-reviewed literature. Research topics may include: The development of data sets with agreed variables to measure outcomes such as: the impact of adjuvant therapy on time to relapse, and identification of clinical, immunological and genetic factors predictive of good/poor response to rituximab K9.5-9.6 None identified.

	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*	K 9.7 A standard data set needs to be developed by the specialist centres (see K9.2-9.4)
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) L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.1 There are a network of expert providers in designated centres. Most cases are dealt with remotely (referring dermatologist sends clinical history, blood and skin biopsy for specialised immunohistochemistry and clinicopathological correlation). L1.2 No change anticipated.
L2 Geography & Access	L2.1 Where do current referrals come from? L2.2 Will the new policy change / restrict / expand the sources of referral? L2.3 Is the new policy likely to improve equity of access? L2.4 Is the new policy likely to improve equality of access / outcomes?	L2.1 Secondary care consultant, usually a dermatologist L2.2 No change anticipated L2.3-2.4 New policy likely to improve equity and equality of access by routinely commissioning treatment for the cohort of patients with pemphigus and pemphigoid across England.
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? L3.2 Is there a change in provider physical infrastructure required?	L3.1 Usual lead in time after a policy is agreed expected (i.e. notification of pharmacists and other relevant parties of new policy), ensuring the appropriate provider governance is in place. L3.2-3.5 No change anticipated.

	L3.3 Is there a change in provider staffing required? L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place? L3.5 Are there changes in the support services that need to be in place? L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor) L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers? 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)	L3.6 Specialist centres should be required to collaborate as a network for data collection, standards development, the design of audits and participation in national or international trials of new therapies. This may require the development of a service specification for this patient cohort and process for designating providers. This would be developed to go alongside policy implementation. L3.7 No changes envisioned to L1.1. 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 immediate plans
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 £873.15 (not including VAT) for 500mg/50ml.[xxxii] 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 payable as it is envisaged the drug would be administered in a day case setting.[xxxiii]
	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 The revenue **cost** per patient per year for **rituximab** is estimated at **£6,600.** This is based on: • A dose of 2g of the drug (at c. £4,200 incl. VAT)[xxxiv] • A cost of administering the drug of c. £2,400 (2 day cases at c.

		£1,200 each)[xxxv] For some patients, this would replace current treatment with **earlier lines** of treatment with steroids/immunosuppressants at a very low cost, and for these patients, there would be a **net cost of c. £6,600** per patient.[xxxvi] For some patients, rituximab would replace treatment with IVIg. For these patients, there would be an estimated savings in relation to **IVIg** spared of c. £54,000.[xxxvii] Overall, there would be a **net savings** for patients in this category of c. £47k per patient. For some patients, rituximab would replace treatment with cyclophosphamide/methylprednisolone. For these patients, there would be an estimated savings in relation to cyclophosphamide/methylprednisolone administrations spared of c. £19,000.[xxxviii] Overall, there would be a **net savings** for patients in this category of c. £12k per patient.
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2. The revenue cost per patient in future years depends on the need for retreatment. Patients on rituximab may require retreatment after 12 - 24 months.[xxxix]
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 Cost saving. In 2016/17, the estimated cost saving is c. £0.2m (assuming 50% part year effect). In 2017/18, it is estimated at c. £0.5m. This is based on an eligible population of c. 200 (of which 90% receives rituximab), assuming yearly retreatment with rituximab. The net figures set out here include a net savings of c. £1.8m in 2017/18 for patients that avoid IVIg, and a cost pressure of c. £1.3m in the same year for patients that had been poorly controlled on earlier lines of treatment who would gain access to the treatment. It should be noted that the level of net savings that could be generated is highly sensitive to the number of IVIg replacement patients and that the figures used for the impact assessment are based on estimates from clinicians and not evidenced actual activity data. There is therefore the possibility of either higher savings or conversely net costs should the actual number of patients in the IVIg cohort be materially different from those assumed in this analysis.

	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 No costs to other parts of the NHS were identified.
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole?	M4.2 Cost saving as set out in M3.1. In 2016/17, the estimated cost saving is c. £0.2m (assuming 50% part year effect). In 2017/18, it is estimated at c. £0.5m.
	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 / public sector funders?	M4.4 No costs or savings for other funders were identified.
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 data in relation to patients with immunobullous diseases is based on estimates rather than registry data. The target population and the fraction of the target population on different treatments might therefore be have not been validated, and could be higher than estimated. There is also a risk that a high number of patients using earlier lines of treatment would be considered for rituximab earlier than they would be considered for comparator treatments (cyclophosphamide, IVIg) under the

		current commissioning policy, and that use of these treatments would not be reduced. This could create a cost pressure if not closely managed. [xl]
	M6.2 Can these be mitigated, if so how?	M6.2 A prior approval software platform could be used to ensure rituximab is used at the correct point in the pathway, and trend analysis could be used to assess whether the correct questions are being asked to ensure proper use within the policy.[xli]
	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 cost savings associated with this policy assume that some patients would substitute away from IVIg or cyclophosphamide under the policy. If this were not the case (i.e. if there was no reduction of IVIg or cyclophosphamide under the policy), there could be a cost pressure of c. 1.25m in 2017/18 if 200 patients took up the treatment and required retreatment.
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*	M7.1 There was a lack of relevant cost effective studies identified. However, Heelam et al., 2015 provided a view on the healthcare cost impact of adding rituximab in the treatment regime in Canadian setting in 2013 based on healthcare utilisation data from 89 patients receiving rituximab for pemphigoid and pemphigus disorders. The majority (84%) of patients were in pemphigus vulgaris subgroup. The results show that there was 30.3% decrease in direct healthcare costs (admissions, outpatient and home visits, investigations etc) with the introduction of rituximab infusion in the treatment regime at a median duration of 28 months (1-256 months) from the time of biopsy diagnosis. The 6 month pre-rituximab costs was $3.8 million and in the 6 months post-rituximab it was $2.6 million. The cost per patient was $42,000 in the 6 months pre-rituximab and $29,000 in the 6 months post-rituximab. Intravenous immunoglobulins (IVIG) was reported as the main cost driver representing 96% of the overall cost prior to rituximab infusion and 63% of the cost following rituximab administration.
	M7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of*	M2.7 The costing analysis did not include information on number of important factors including calculation of adverse events secondary to standard treatment versus rituximab. The costs of prophylactic medications

	evidence	in conjunction with corticosteroids (e.g., proton pump inhibitors, bisphosphonates) are not included in this analysis.
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 Not applicable. M8.2 Not applicable.

[i] This is based on an estimated prevalence of 105 per million population as set out in the policy proposition and multiplying this by the population in England, based on ONS population data. For the incidence figures, see Policy Proposition and Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J., "Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study." *in* BMJ. 2008 Jul 9;337, available at http://www.bmj.com/content/337/bmj.a180, last accessed: 23/11/2015. Using incidence figures from this source, the prevalence of 105pmp was calculated by the policy working group as follows: an incidence of 0.7 / 100,000 patient years implies an incidence of 7 per million patient years; assuming a population in England of 54m yields 378 new patients per year; with a median duration of 15 years, the prevalence is estimated at 5,670; and the prevalence pmp is estimated at 105 pmp.

[ii] This is based on an estimated prevalence of 215 per million population as set out in the policy proposition and multiplying this by the population in England, based on ONS population data. For the incidence figures, see Policy Proposition and Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J., "Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study." *in* BMJ. 2008 Jul 9;337, available at http://www.bmj.com/content/337/bmj.a180, last accessed: 23/11/2015. Using incidence figures from this source, the prevalence of 215 pmp was calculated by the policy working group as follows: an incidence of 4.3 / 100,000 patient years implies an incidence of 43 per million patient years; assuming a population in England of 54m yields 2322 new patients per year; with a median duration of 5 years, the prevalence is estimated at 11,610; and the prevalence per million population is estimated at 215 pmp.

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

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

[v] Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J., "Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study." *in* BMJ. 2008 Jul 9;337, available at http://www.bmj.com/content/337/bmj.a180, last accessed: 23/11/2015.

[vi] NHS Choices, http://www.nhs.uk/conditions/Pemphigus-vulgaris/Pages/Definition.aspx, last accessed: 06/01/2016.

[vii] NHS Choices, http://www.nhs.uk/Conditions/epidermolysis-bullosa/Pages/introduction.aspx, last accessed: 23/11/2015.

[viii] Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J., "Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study." *in* BMJ. 2008 Jul 9;337, available at http://www.bmj.com/content/337/bmj.a180, last accessed: 23/11/2015.

[ix] Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J., "Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study." *in* BMJ. 2008 Jul 9;337, available at http://www.bmj.com/content/337/bmj.a180, last accessed: 23/11/2015.

[x] As set out in the policy proposition

[xi] Based on discussions with the policy working group and experience of clinicians with an interest in immunobullous disease. . This is a high level estimate; the percentage could be higher depending on local clinical practice.

[xii] Based on discussions with policy working group. IVIg is administered typically in over 3 to 5 day cases. It could be used for longer periods than three to six months.

[xiii] Based on discussions with the policy working group, 2% to 5% of the target population are treated with cyclophosphamide and methylprednisolone. This is a high level estimate; the percentage could be higher depending on local clinical practice.

[xiv] Based on discussions with policy working group.

[xv] Based on discussions with policy working group.

[xvi] National IFR database. Data for 2015/16 covers April to September 2015. Excludes requests withdrawn, redirected, or considered at pre-screening stage. Based on discussions with the policy working group, the number of requests submitted pre-screening is estimated to be high.

[xvii] The general population growth rate has been used as a conservative estimate. While evidence suggesting higher growth rates was found in Langan SM. Et. al. (2008), others suggest little growth (see: Saha, M. et. al., Rapid response to Langan SM et. al. (2008), available at http://www.bmj.com/content/337/bmj.a180/rapid-responses, last accessed: 07/01/16). The growth rate used is based on ONS data, weighted for the relative age and gender factors as set out in K1.4 in relation to the prevalent populations of pemphigoid and pemphigus.

[xviii] Based on ONS growth rates applied to the prevalence figures set out in K1.1. Figures are rounded.

[xix] Based on ONS growth rates applied to the target population figure set out in K1.2. Figures are rounded.

[xx] Based on ONS growth rates applied to the activity figure set out in K1.5. Figures are rounded.

[xxi] Based on ONS growth rates applied to the activity figure set out in K1.5. Figures are rounded.

[xxii] See policy proposition

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

[xxiv] This constitutes the 50% phasing assumption. Based on discussions with the policy working group.

[xxv] Figures rounded.

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

[xxvii] Figures rounded.

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

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

[xxx] See K9.

[xxxi] In the SUS dataset, the following codes were used to identify activity related to rituximab (OPCS code X892) for immunobullous diseases (ICD-10 codes: L100 for pemphigus vulgaris; L120 for bullous pemphigoid; L123 for acquired epidermolysis bullosa).

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

[xxxiii] Based on discussions with NHS England pharmacists and finance leads. Section 3.2, When can goods being provided on prescription be zero-rated for VAT purposes? https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products/vat-notice-70157-health-professionals-and-pharmaceutical-products

[xxxiv] Based on the price set out in M1.3

[xxxv] Estimate based on costed SUS data at 2014/15 tariff in relation to the administration of monoclonal antibodies in a day case setting for patients with immunobullous disease diagnosed within the first three ICD-10 fields.

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

[xxxvii] Based on a dose of 2g/kg of the drug (at £42.50 per gram) per course [Sources: http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=19805211000001108&toc=nofloat; Department of Health. (2011). Clinical Guidelines for Immunoglobulin use, 2nd edition. Available at: http://www.ivig.nhs.uk/documents/dh_129666.pdf, last accessed: 17 February 2016], and a cost of administering the drug of c. £1,490 per day case [Based on analysis of SUS data costed at 2014/15 prices in relation to OPCS X961 (Immunoglobulins, band 1) for patients with a diagnosis relating to immunobullous disease in the first three positions], with 3-5 day cases per course. An average treatment duration of 3 to 6 months as per discussions with the policy working group.

[xxxviii] A dose of 1g of cyclophosphamide per month, at a cost of £11.60 (incl. VAT) and a dose of 1.5-3.0g of methylprednisolone per month, at a cost of £46.70 (incl. VAT). Assumes a cost of administering cyclophosphamide/methylprednisolone of c. £1,000 per day case, with c. 3 day cases per month. Assumes a duration of 3 to 6 months.

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

[xl] Based on discussions with the policy working group and finance lead.

[xli] Based on discussions with the policy working group and finance lead.