Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	A06X03		
Policy Title	Interim Clinical Commissioning Policy Statement: Eculizumab in the treatment of recurrence of C3 glomerulopathy post-transplant		
Accountable Commissioner	Jon Gulliver	**Clinical Lead**	Alison Rylands
Finance Lead	Craig Holmes	**Analytical Lead**	Jay Emin
Section A - Activity Impact			
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)	
A1 Current Patient Population & Demography / Growth	A1.1 What is the prevalence of the disease/condition?	A1. 1 C3G is a rare disease with an estimated prevalence of 1-2 cases per million in the UK [Medjeral-Thomas et al, 2014].	
	A1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	A1.2 Figures provided by NHSBT show that in the past ten years 39 patients with dense deposit disease (DDD) have been transplanted. In the same period 3 patients with DDD have lost their transplant to recurrent disease. There are a total of 59 patients in the UK with a functioning kidney transplant whose primary renal disease is said to be DDD and there are currently 6 patients on the active waiting list. From the available published information we estimate that 70% of patients at some stage will develop recurrent disease and that a maximum of 50% of patients with	

		recurrent disease will meet the above criteria. **Whilst the information available from NHSBT may be subject to underreporting we estimate that fewer than 5 patients per year will meet the above criteria.**
	A1.3 What age group is the treatment indicated for?	A1.3 All age groups.
	A1.4 Describe the age distribution of the patient population taking up treatment?	A1.4 All age groups.
	A1.5 What is the current activity associated with currently routinely commissioned care for this group?	A1.5 Due to its rarity it is difficult to estimate the current activity associated with the care of this patient group. The typical treatment modalities are outlined below. Refractory C3G refers to declining renal function that is unresponsive to typical immunosuppressive modalities utilised to treat glomerulonephritis. These include glucocorticoid therapy (oral or pulse treatment), mycophenolate mofetil, tacrolimus, cyclophosphamide and rituximab. In patients with rapidly deteriorating renal function plasma exchange has been utilised. None of these approaches alone, or in combination, have proven to be widely effective in the treatment of C3G. Consequently many patients with C3G develop refractory disease in either the native or transplant kidney.
	A1.6 What is the projected growth of the disease/condition prevalence (prior to	A1.6 **The incidence of C3 glomerulopathy is 1–2 per million population per year.** There are a total of 59 patients in the UK with a

	applying the new policy) in 2, 5, and 10 years?	functioning kidney transplant whose primary renal disease is said to be DDD and there are currently six patients on the active waiting list **An estimated maximum of 5 cases per year will meet the clinical criteria for eculizumab.** Growth is very unlikely to be linear, i.e. a cohort that grows by up to 5 patients per annum. However, fixing on a number is very difficult given the clinical uncertainty about how many of the patients will respond, and therefore might go on to be re-treated at some point, and those that will not respond.
	A1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years?	A1.7 See A5.1. Incidence is estimated at 5 new cases per year who will require established treatment options as outlined above. However, the condition has a poor prognosis with 10 year renal survival of approximately 50% in most cases.
	A1.8 How is the population currently distributed geographically?	A1.8 National
A2 Future Patient Population & Demography	A2.1 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?	A2.1 The policy adds a new treatment for refractory disease.

	A2.2 Please describe any factors likely to affect growth in the patient population for this intervention (e.g. increased disease prevalence, increased survival).	A2.2 Increased disease prevalence and increased survival.
	A 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.	A2.3 No
	A2.4 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?	A2.4 **An estimated maximum of 5 cases per year will meet the clinical criteria for eculizumab.** Growth is very unlikely to be linear, i.e. a cohort that grows by up to 5 patients per annum. However, fixing on a number is very difficult given the clinical uncertainty about how many of the patients will respond, and therefore might go on to be re-treated at some point, and those that will not respond.
A3 Activity	A3.1 What is the current annual activity for the target population covered under the new policy? Please provide details in accompanying excel sheet.	A3.1 Within Internal Activity and Cost Template.
	A3.2 What will be the new activity should the new / revised policy be implemented in the target population? Please provide details	

	in accompanying excel sheet. A3.3 What will be the comparative activity for the 'Next Best Alternative' or 'Do Nothing' comparator if policy is not adopted? Please details in accompanying excel sheet.	
A4 Existing Patient Pathway	A4.1 If there is a relevant currently routinely commissioned treatment, what is the current patient pathway? Describe or include a figure to outline associated activity. A4.2. What are the current treatment access criteria? A4.3 What are the current treatment stopping points?	Refractory C3G refers to declining renal function that is unresponsive to typical immunosuppressive modalities utilised to treat glomerulonephritis. These include glucocorticoid therapy (oral or pulse treatment), mycophenolate mofetil, tacrolimus, cyclophosphamide and rituximab. In patients with rapidly deteriorating renal function plasma exchange has been utilised. None of these approaches alone, or in combination, have proven to be widely effective in the treatment of C3G. Consequently many patients with C3G develop refractory disease in either the native or transplant kidney.
A5 Comparator (next best alternative treatment) Patient Pathway	A5.1 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. A5.2 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.	
A6 New Patient Pathway	A6.1 Describe or include a figure to outline associated activity with the patient pathway for the proposed new policy.	A6.1 NHS England will, therefore, commission eculizumab for the treatment of recurrent disease post-transplant in patients with C3 glomerulopathy **only if all** the following clinical criteria are met. a. A primary renal diagnosis of C3 glomerulopathy confirmed by renal biopsy including light microscopy, immunofluorescence and electron microscopy. b. Recurrent disease occurring at any time post-transplant. c. Recurrent disease characterised on biopsy by an active glomerulonephritis with cellular crescents. Histopathology will be reviewed by a single centre with expertise in the pathology of C3 glomerulopathy. d. Evidence of glomerular C9 deposition on transplant biopsy. e. Evidence at the time of recurrence of a significant

		decline of transplant function (>20% decline in eGFR) within the previous three months. This criteria will not be necessary if the recurrence occurs immediately after transplantation when transplant function has not yet been established. f. No other cause for the decline in transplant function can be identified.
	A6.2 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.	A6.2 If all these criteria are met then eculizumab should be started using the same dose as recommended for the treatment of atypical haemolytic uraemia syndrome (at www.rarerenal.org). We recommend that treatment be continued for 4 months. The possible outcomes at or before this time are a. Loss of the transplant despite treatment. b. Ongoing deterioration in graft function (eGFR) with no evidence of a response to treatment c. Stabilisation of graft function (eGFR). d. An improvement in graft function (eGFR). For a. and b. eculizumab will be withdrawn and not reintroduced. For c. and d. eculizumab will also be withdrawn after 4 months of treatment but will be reintroduced for a further four month period if there is a subsequent deterioration in graft function (of a similar magnitude to that defined by criteria e.) which on biopsy is shown to be due to active recurrent disease. Again there should be no other identifiable cause for the decline in transplant function.
A7 Treatment Setting	A7.1 How is this	A7.1 It is proposed to deliver the service

	treatment delivered to the patient? ○ Acute Trust: Inpatient/Daycase/ Outpatient ○ Mental Health Provider: Inpatient/Outpatient ○ Community setting ○ Homecare delivery A7.2 Is there likely to be a change in delivery setting or capacity requirements, if so what? *e.g. service capacity*	locally to patients but with decision making agreed through a single named expert centre. A7.2 No
A8 Coding	A8.1 In which datasets (e.g. SUS/central data collections etc.) will activity related to the new patient pathway be recorded? A8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	A8.1 Excluded drugs monitoring per normal contract arrangements
A9 Monitoring	A9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule? A9.2 If this treatment is a drug, what pharmacy	N/A

	monitoring is required? A9.3 What analytical information /monitoring/ reporting is required? A9.4 What contract monitoring is required by supplier managers? What changes need to be in place? A9.5 Is there inked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring? A9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy? A9.7 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*	
Section B - Service Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
B1 Service	B1.1 How is this	B1.1 Tertiary centres.

Organisation	service currently organised? (i.e. tertiary centres, networked provision) B1.2 How will the proposed policy change the way the commissioned service is organised?	 B1.2 It is proposed to deliver the service locally to patients but with co-ordination from an expert centre.
B2 Geography & Access	B2.1 Where do current referrals come from? B2.2 Will the new policy change / restrict / expand the sources of referral? B2.3 Is the new policy likely to improve equity of access? B2.4 Is the new policy likely to improve equality of access / outcomes?	B2.1 Transplant and renal centres B2.2 No B2.3 Yes B2.4 Yes
B3 Implementation	B3.1 Is there a lead in time required prior to implementation and if so when could implementation be achieved if the policy is agreed? B3.2 Is there a change in provider physical infrastructure required? B3.3 Is there a change in provider staffing	B3.1 Immediate B3.2 No B3.3 No

	required?	
	B3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	B3.4 No
	B3.5 Are there changes in the support services that need to be in place?	B3.5 No
	B3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	B3.6 Yes, requirement for supervision and sign off by national lead centre.
	B3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	B3.7 No change.
	B3.8 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)	B3.8 Publication and notification of new policy.
B4 Collaborative Commissioning	B4.1 Is this service currently subject to or planned for	B4.1 No

	collaborative commissioning arrangements? (e.g. future CCG lead, devolved commissioning arrangements)	
Section C - Finance Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
C1 Tariff	C1.1 Is this treatment paid under a national prices*, and if so which?	C1.1 No
	C1.2 Is this treatment excluded from national prices?	C1.2 Yes
	C1.3 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?	C1.3 No
	C1.4 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?	C1.4 N/A
	C1.5 is VAT payable (Y/N) and if so has it been included in the costings?	C1.5 Yes

	C1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	C1.6 Prescribing to be authorised via national centre subject to clinical criteria.
C2 Average Cost per Patient	C2.1 What is the revenue cost per patient in year 1?	C2.1 Assuming patient requires 2 x 4 month cycles of Eculizumab plus ongoing immunosuppression the total cost is £308k. For best case scenario if the patient does not deteriorate and only 1 x 4 month treatment required then annual cost is £157k. Dialysis costs are avoided circa £45k, so net cost is £263k (best case £112k) where treatment is successful and patient doesn't return to dialysis.
	C2.2 What is the revenue cost per patient in future years (including follow up)?	C2.2 Probable scenario is where patient requires 2 x 4 month doses of Eculizumab in year 1 only. In future years, costs will be restricted to ongoing immunosuppression at £6k per year. Dialysis costs avoided circa £45k, so net saving of £39k.
C3 Overall Cost Impact of this Policy to NHS England	C3.1 Indicate whether this is cost saving, neutral, or cost pressure to NHS England.	C3.1 There is a potential range depending on patient response to treatment but for probable scenario where patient requires 2 x 4 month Eculizumab treatment in the first year only this would be a net cost increase of £1.3m each year above the cost of the current pathway. In a best case scenario if all patients are stabilized after 1 x 4 month treatment of Eculizumab with no further deterioration thereafter this treatment would be cost neutral by year 4 compared with ongoing cost of dialysis (and other complications) and would deliver cost savings thereafter. The best case scenario would be an initial cost increase with savings in later years (Yr 1 +£0.6m, Yr 2 +£0.4m, Yr 5 -£0.2m reduction). It should be noted however, this scenario is unlikely and conversely

		there is a risk of costs higher than the probable scenario if some patients require further cycles of treatment after the first year where it is demonstrated that Eculizumab had been effective in stabilizing their condition but they have subsequently deteriorated.
	C3.2 Where this has not been identified, set out the reasons why this cannot be measured.	C3.2 Likelihood that actual position will be between probable and best case scenarios but difficult to be precise without evidence of ongoing effectiveness and accuracy on patient numbers and noting risks that some patients may require further treatment in future years.
C4 Overall cost impact of this policy to the NHS as a whole	C4.1 Indicate whether this is cost saving, neutral, or cost pressure for other parts of the NHS (e.g. providers, CCGs).	C4.1 As above
	C4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole.	C4.2 As above
	C4.3 Where this has not been identified, set out the reasons why this cannot be measured.	C4.3 As above
	C4.4 Are there likely to be any costs or savings for non NHS commissioners / public sector funders?	C4.4 N/A
C5 Funding	C5.1 Where a cost pressure is indicated,	C5.1 Specialised commissioning recurrent funding envelope.

	state known source of funds for investment, where identified. *e.g. decommissioning less clinically or cost-effective services*	
C6 Financial Risks Associated with Implementing this Policy	C6.1 What are the material financial risks to implementing this policy?	C6.1 Potential range in cost impact due to uncertainty around total patient volumes and the proportion of patients requiring ongoing repeated treatments.
	C6.2 Can these be mitigated, if so how?	C6.2 Ongoing review using evidence to develop future forecasting of impact if policy adopted.
	C6.3 What scenarios (differential assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	C6.3 Accompanying financial model describes probable maximum case (cost impact +£1.3m). Separate modelling of best case produced indicates a £3.2m annual saving by year 10 due to avoided dialysis costs and other inpatient activity related to complications. However, likely scenario is somewhere between these, depending on age profile of patient cohort and differing degrees of responsiveness to the treatment and patient eligibility as condition progresses.
C7 Value for Money	C7.1 What evidence is available that the treatment is cost effective? *e.g. NICE appraisal, clinical trials or peer reviewed literature*	C7.1 Case reports and series of the use of Eculizumab in C3G include its use in *de novo* disease and in recurrent disease in the renal transplant. These are all Scottish Intercollegiate Guideline Network (SIGN) levels of evidence grade 3 (non-analytical studies). With the exception of one open label uncontrolled trial, these consist of case reports. There is no controlled clinical trial data on the use of eculizumab in C3G and it is not licensed for the treatment of C3G. Case reports and series of the use of Eculizumab in C3G include its use in *de novo* disease and in recurrent disease in the renal transplant. These are all

		Scottish Intercollegiate Guideline Network (SIGN) levels of evidence grade 3 (non-analytical studies). With the exception of one open label uncontrolled trial, these consist of case reports. There is no controlled clinical trial data on the use of eculizumab in C3G and it is not licensed for the treatment of C3G. These recommendations are SIGN level Grade D.
	C7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of evidence*	
C8 Cost Profile	C8.1 Are there non-recurrent capital or revenue costs associated with this policy? *e.g. Transitional costs, periodical costs*	C8.1 No
	C8.2 If so, confirm the source of funds to meet these costs.	C8.2 N/A