Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	A03X03		
Policy Title	Pasireotide: An injectable medical therapy for the treatment of Cushing's 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	K1.1 What is the prevalence of the disease/condition?	K1.1 This is a policy to **routinely commission** the use of pasireotide for certain patients with Cushing's disease. Cushing's disease is a sub-type of Cushing's syndrome, which is caused by a pituitary adenoma releasing high levels of adrenocorticotropic hormone (ACTH). It is estimated that the prevalence is around 40 per million,[i] or around 2,200 people affected in England in 2014/15.[ii] The incidence of the disease is estimated at around 1 to 2 people per million, which corresponds to approximately 55 to 110 people diagnosed every year in England.[iii]
	K1.2 What is the number of patients currently eligible for the treatment under the proposed	K1.2 The target population for pasireotide comprises those with Cushing's disease who do not respond to (or are not suitable for)

	policy?	pituitary surgery and cannot tolerate the existing pharmacological treatments. Pasireotide would only be taken for a limited time while patients were waiting for curative therapy to be effective. This population is estimated to be in the region of 5-10 patients per year in 2014/15, or around 10% of the incident population.[iv] It is estimated that there would be no backlog of patients waiting for this policy as Cushing's disease cannot go untreated.
	K1.3 What age group is the treatment indicated for?	K1.3 The policy indicates pasireotide for use in adults (over 18 years).
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 Cushing's disease can affect any age group. However, it is five times more common in women than in men.[v] It is more prevalent in those aged 20 to 50.[vi]
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 Pasireotide is not currently routinely commissioned for Cushing's disease. Pasireotide is a drug that is taken for a limited duration (c. 21 months, in addition to the initial 2 months of trial)[vii] while patients wait for curative therapy to become effective.[viii] Currently, only very few patients may have access to **pasireotide**. Three individual funding requests (IFRs) for the drug were submitted in 2014/15, whilst 2 IFRs were submitted in the first half of 2015/16.[ix] The current activity is estimated at up to 5 new patients in the last 18 months, although this cannot be confirmed.[x] It is estimated that without pasireotide, all the patients in the eligible population would undergo **adrenalectomies**. They would

		then require lifelong treatment with glucocorticoid and mineralocorticoids.[xi]
	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 Cushing's disease is a heterogeneous disorder that affects a small cohort of patients,[xii] with no disease-specific growth rate identified. However, the prevalence would grow in line with demographic growth, and it is estimated that the future prevalence of Cushing's disease will be in the region of:[xiii] • 2,220 persons in 2016/17 • 2,230 persons in 2017/18 • 2,270 persons in 2020/21 As pasireotide is taken for a limited duration at a certain point in the pathway, the incidence figures are more relevant to understanding activity. It is estimated that the incidence in future will be in the region of: [xiv] • 56 to 112 in 2016/17 • 56 to 112 in 2017/18 • 57 to 114 in 2020/21 Of these, an estimated 5 to 10 per year would be eligible for pasireotide as set out in K1.2.[xv]
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2, 5 and 10 years?	K1.7 While there may have been up to 5 IFRs submitted in the past 18 months, the number of IFRs approved is unknown. Without routine commissioning, in future years, new patients would only receive the treatment on an exceptional basis under IFR – this would be a very small number (less than 5 per year). In the 'do nothing' case it is expected that the number of adrenalectomies per year would grow in line with the population as no other changes to the patient pathway were identified.[xvi] The number of **adrenalectomies** is estimated in the region of:

		• 5 to 10 in 2016/17 • 5 to 10 in 2017/18 • 5 to 10 in 2020/21 These patients would also be receiving **steroids** for life as set out in K1.5. The patients receiving steroids in each year is estimated to grow as more patients undergo adrenalectomies each year. For the eligible population from Y1 onwards, this is estimated to be in the region of: • 5 to 10 in 2016/17 • 10 to 20 in 2017/18 • 25 to 50 in 2020/21
	K1.8 How is the population currently distributed geographically?	K1.8 Across England - based on the evidence reviewed, no significant geographical differences 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 The new policy adds an additional line of treatment to the patient pathway for Cushing's disease.
	K2.3 Please describe any factors likely to affect growth in the patient population for this intervention (e.g. increased disease prevalence, increased survival)	K2.2 As noted in K1.6, Cushing's disease is a heterogeneous disorder that affects a small cohort of patients, with no disease-specific growth rate identified.
	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 None identified.
	K2.4 What is the resulting expected net increase or decrease in the number of patients who will access the treatment per	K2.4 There would be a **net increase** in the number of patients accessing the treatment each year under the policy. As compared to the 'do nothing' scenario, the additional number of

	year in year 2, 5 and 10?	patients starting treatment is estimated in the region of 5 to 10 each year: [xvii] The 5 - 10 patients accessing the treatment each years is the steady state, and it is not expected to grow significantly in the next five years as the growth rate of the condition is very low (please see K1.7). Activity in relation to the treatment is **cumulative** over a period of c. 21 months.[xviii]
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 for the target population is set out in question K1.5; of the 5 – 10 patients per year in the target population, up to 5 patients may be receiving pasireotide, and the remainder are estimated to have undergone adrenalectomies. K3.2 *Please see the **Appendix** for a diagram illustrating the new activity described here*. Under the policy, the number of patients treated each year with **pasireotide** is estimated to be in the region of: [xix] [xx] • 5 - 10 individuals actively on pasireotide in 2016/17 assuming treatment lasts an average of 21 months for those that respond after two months 2016/17 • 7 - 17 individuals actively on pasireotide in 2017/18 assuming treatment lasts an average of 21 months for those that respond after two months. • 7 - 17 in 2020/21 assuming treatment lasts an average of 21 months for those that respond after two months. The low estimate of 7 is based on a low scenario where the population to be trialled on the medication is 5 per year, and only 29%[xxi] of patients improve after the initial 2 months – the remainder therefore stop receiving treatment. The high estimate is based on ~10 patients, with 67% receiving treatment for an average of 21 months.[xxii] The number of patients actively on the drug exceeds the eligible population of ~10 because patients can be on the drug for several years. There would also be two

		additional outpatient appointments related to the therapy Around 46% of patients on pasireotide are estimated to develop side effects that require **glucose lowering drugs** (while they are on the pasireotide).[xxiii] Based on the levels of pasireotide noted above, around 1 to 6 patients per year could require these drugs. Because pasireotide enables patients to move into a radiotherapy pathway[xxiv] this may **change activity in other ways**. In particular: • In each year, patients would generally be given radiotherapy as curative treatment. The regimen for these patients is estimated at 25-28 fractions of **external beam radiotherapy** (EBRT) each.[xxv] The activity would therefore be in the range of 40 to 190 outpatient attendances for EBRT each year, and 2 to 10 planning sessions for EBRT.[xxvi] This would be activity not seen in the 'do nothing' case. It is possible that some patients would be eligible for stereotactic radiosurgery as an alternative to fractionated therapy.[xxvii] • For patients undergoing EBRT, an estimated 30% to 70% would develop **hypopituitarism**,[xxviii] requiring lifelong medical treatment, including levothyroxine, desmopressin and hydrocortisone. For some patients where pasireotide is trialled but not effective (up to 71% of cases) or radiotherapy is not effective (circa 22% of cases),[xxix] **adrenalectomies** would be a curative option. It is estimated that under the new pathway, up to 8 patients per year could require adrenalectomies having failed at earlier stages.[xxx] These patients would require lifelong hormone therapy as set out in K1.5. There is expected to be a lower number of adrenalectomies overall, as a result of radiotherapy.
	K3.3 What will be the comparative activity for the 'Next Best Alternative' or 'Do Nothing'	K3.3 The 'do nothing' scenario refers to current activity, assumed to be the 'steady state' rolled forward in future years.

	comparator if policy is not adopted? Please details in accompanying excel sheet	The future activity levels are therefore set out in K1.7; of the 5 – 10 patients per year in the target population, up to 5 patients may be receiving pasireotide, and the remainder are estimated to have undergone adrenalectomies.
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. K4.2. What are the current treatment access criteria? K4.3 What are the current treatment stopping points?	K4.1 Refer to the patient pathway included in the appendix. K4.2 Patients who may benefit from metyrapone or ketoconazole would only be prescribed treatment when it has been established that a curative therapy such as radiotherapy or pituitary surgery is planned or in progress. K4.3 Treatment would be stopped if any adverse events occurred, or if treatment was no longer effective, measured by outcomes such as cortisol levels.
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.	K5.1-5.2 For patients unable to tolerate metyrapone and ketoconazole, the only treatment option currently available is adrenalectomy. (See Appendix for pathway comparison)
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	K6.1-6.2 In all cases where medical therapy is prescribed, pasireotide is proposed as a second line treatment where metyrapone and ketoconazole have not been tolerated or are not clinically effective. Pasireotide should only be used for a defined period for patients who are on a curative pathway - for example patients who are waiting for radiotherapy treatment to become effective or require additional condition management prior to

	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.	surgery. The current licenced indication is for a two month initial period with regular monitoring of cortisol levels to ensure continued efficacy during and beyond this initial phase.
K7 Treatment Setting	K7.1 How 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 It is proposed that the drug is delivered from an acute Trust specialised endocrinology centre.[xxxi] It is delivered in an outpatient setting. K7.2 None identified.
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 Pasireotide is a high cost drug excluded from tariff, so it should be captured in the high cost drug dataset for routine commissioning.[xxxii] 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? K9.2 If this treatment is a drug, what	K9.1 The Information Schedule should be updated to include a requirement for pasireotide data to be collected in Blueteq K9.2 None identified. See K9.1 for monitoring arrangements.

	pharmacy monitoring is required?	
	K9.3 What analytical information /monitoring/ reporting is required?	K9.3 Clinicians will be required to record both short term and long term outcomes of individuals with Cushing's disease who receive pasireotide, including consistent monitoring of the patients' cortisol levels.
	K9.4 What contract monitoring is required by supplier managers? What changes need to be in place?	K9.4 Pasireotide usage should be monitored via Blueteq to ensure starting criteria are met.
	K9.5 Is there linked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring?	K9.5 Not applicable.
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.6 Not applicable.
	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 Blueteq or similar should be used to capture the starting and stopping points (and rationale) for all patients who receive pasireotide.
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 Through specialised endocrinology centres (See service specification for Specialised Endocrinology).
	L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.2 No change anticipated.
L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 The adult specialist endocrinology service should consist of a multi-professional group with specialist experience in treating site-specific endocrine disease. Not all centres will have all the skills and expertise required to deliver all specialist endocrinology services. It is important that the core multi-professional group reviews all new cases referred to the
	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?	specialist service. L2.2 – 2.4 The new policy is likely to improve equality of access and outcomes by ensuring consistent prescription of pasireotide.
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? L3.3 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)	L3.1 No more than expected for a new treatment option. L3.2 – L3.7 None anticipated. L3.8 Not applicable.

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)	This service is not currently the subject of any proposal to change the commissioning arrangements.
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?	M.1.2 Pasireotide is a high cost drug excluded from tariff.
	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 As an excluded drug, the price is subject to local negotiations. The list price is £3,240 for 60 1ml ampoules of 0.6mg each (excl. VAT). The price is the same for 60 1ml ampoules of 0.9mg each, or around £54 per vial.[xxxiii] For the yearly cost of the drug, see 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 The drug is provided by Trusts As such, VAT would not be recoverable.[xxxiv] VAT is included in the calculations sections M2 and M3.
	M1.6 Do you envisage a prior approval / funding authorisation being required to	M1.6 No

	support implementation of the new policy?	
M2 Average Cost per Patient	M2.1 What is the revenue cost per patient in year 1?	M2.1 For patients that are successful on pasireotide, in year 1 the cost of treatment is estimated at approximately £47.3k (incl. VAT) if the drug were taken for the full year.[xxxv] There would be minimal costs for outpatients at an estimated £202 (£101 per appointment).[xxxvi] The drug would be stopped after the initial two months if the treatment is ineffective,[xxxvii] in which case the cost per patient for the drug could be £7,900. This could apply to a significant number of patients.[xxxviii] Please see the appendix for **further information on the pathway** and the associated costs.[xxxix]
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 This drug is intended for use before curative treatments become effective.[xl] The cost of this drug per patient per year therefore depends on the length of time before other treatments take effect.[xli] While the unit cost per month of treatment would remain the same in year two, patients may only use the drug for part of the year,[xlii] leading to a lower annual cost. Note that in the 10-year horizon considered, no changes to the price of pasireotide are expected.[xliii]
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 pressure. In 2016/17 the annual net cost[xliv] is estimated to be in the range of £50k (with 5 patients in the population and 29% of these patients using pasireotide for 21 months)[xlv] to £170k in 2016/17 (with 10 patients in the population, and a 67% success rate of pasireotide). The 'mid cost' scenario has an estimated net cost of £120k (with 7.5 patients, and a 67% success rate of pasireotide).[xlvi] In 2020/21 when there is full year effect, the cost is estimated at £500 (range estimate £170k to £660, based on the same range of inputs). No backlog of patients is expected as past patients would have

		undergone an adrenalectomy and therefore would not require pasireotide. It is assumed that the policy would be gradually phased in, such that in 2015/16 50% of the target population would receive pasireotide, whilst the remainder would follow the current pathway and undergo adrenalectomies.
	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 Cost benefit. For CCGs, in 2016/17 this could range from £5k to £20k in 2016/17. The 'mid cost' scenario has an estimated net benefit of £15k. This is mainly due to lower expenditure on lifelong drug treatment that fewer patients require after pasireotide + radiotherapy. In year 5 when there is full year effect, the benefit could be £70k (range estimate £20k to £100k, based on the same range of inputs).
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole	M4.2 Cost pressure. In 2016/17 this could range from £43k to £150k in 2016/17. The mid cost scenario has an estimated net cost of £110k. In year 5 when there is full year effect, the cost is estimated at £430k (range £150k to £560k, based on the same range of inputs).
	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	M4.4 No evidence of costs or savings beyond the NHS has been identified.

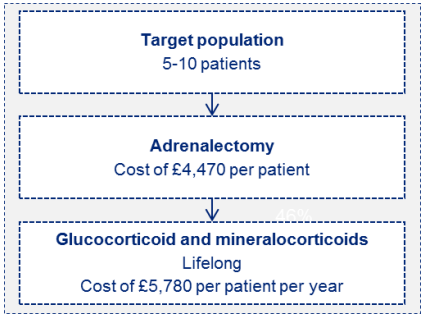
	sector funders?	
`	M5.1 Where a cost pressure is indicated, state known source of funds for investment, where identified e.g. decommissioning less clinically or cost-effective services	M5.1 To be discussed at CPAG.
M6 Financial	M6.1 What are the material financial risks to implementing this policy?	M6.1 The number of patients that respond to pasireotide will affect the cost to NHS England. Different assumptions on the size of the target population have been included in the calculations of the range of the likely cost impact.
	M6.2 Can these be mitigated, if so how?	M6.2 None 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 Three scenarios have been developed to test the base case: The 'high cost' scenario assumes • 10 patients are eligible each year for pasireotide • Pasireotide is effective in 67% of patients[xlvii] The 'mid cost' scenario assumes • 7.5 patients are eligible each year for pasireotide • Pasireotide is effective in 67% of patients[xlviii] The 'low cost' scenario assumes • 5 patients are eligible each year for pasireotide • Pasireotide is effective in 29% of patients All three scenarios assume • An average treatment duration of pasireotide of 21 months (in addition to the initial 2 months trial period. The range is 6 to 36 months) • A failure rate of radiotherapy of 22% (range: 17% to 27%) • 53% of patients for whom radiotherapy was effective need lifelong therapy (range: 30% to 76%)

		The sources for these percentages are set out in the footnotes corresponding to K3.2.
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 There are no published studies evaluating the cost effectiveness of pasireotide. Similarly there are no published studies comparing pasireotide with other drugs used in management of Cushing's Disease or studies evaluating pasireotide in combination with other drugs used in Cushing's Disease. M7.2 Not applicable.
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 No non-recurrent or capital costs have been identified. M8.2 To be discussed at CPAG.

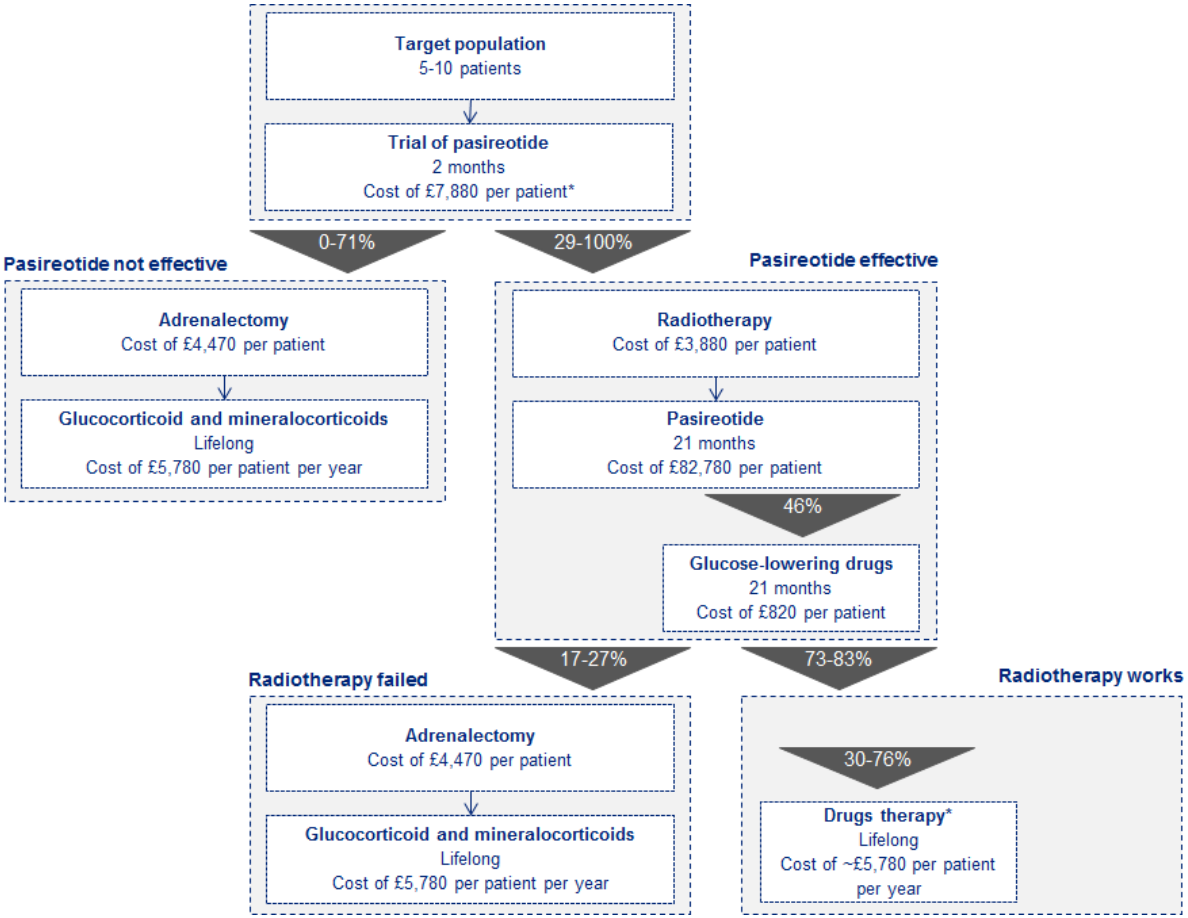
Appendix

For the target population, the graphs below illustrate the patient pathway in relation to pasireotide in both the 'current pathway' and the 'pathway under the policy' proposition. (For sources refer back to the answer to question M2.1 and the footnote xxxix included therein for details about the cost calculations.)

Target population: Current pathway



Target population: Pathway under the policy



*The difference in overall cost is taken to be relatively similar to that of hormone replacement post adrenalectomy as discussed with the working group.

[i] North East Treatment Advisory group, (2012). "Pasireotide for Cushing's disease", NHS Regional Drug & Therapeutics Centre (Newcastle).

[ii] This figure has been calculated by using the prevalence rate of 40 per million and multiplying it by the 2014/15 projected population in England (using Office for National Statistics (ONS) population projection data).

[iii] Clinical Commissioning Policy, "Pasireotide for the treatment of Cushing's disease", March 2014 - NHS England A03/P/c. The range has been calculated using the range of incidence and ONS population data for the population as set out in footnote ii.

[iv] Clinical Commissioning Policy, "Pasireotide for the treatment of Cushing's disease", March 2014 - NHS England A03/P/c Clinical Commissioning Policy: pasireotide for the treatment of Cushing's Disease. March 2014 - NHS ENGLAND A03/P/c. Between 20% and 50% of patients do not respond to initial surgery based on: http://www.nhs.uk/Conditions/Cushings-syndrome/Pages/Treatment.aspx . For those that do not respond to surgery, around 17% may not have sufficient response to Metyrapone. http://www.ncbi.nlm.nih.gov/pubmed/1657460.

[v] Neuroendocrine Clinical Centre (Massachusetts General Hospital and Harvard Medical School), "What are Cushing's syndrome and Cushing's disease?", accessible at: http://pituitary.mgh.harvard.edu/CushingsSyndrome.htm#Causes, last accessed: 09/11/2015.

[vi] 70% of those with Cushing's syndrome are aged 20-50. Cushing's disease accounts for around 70% of cases of Cushing's syndrome in adults, according to American Association of Neurological Surgeons (October 2015), "Patient Information: Cushing's Syndrome/disease", accessible at: http://www.aans.org/Patient%20Information/Conditions%20and%20Treatments/Cushings%20Disease.aspx, last accessed: 09/11/2015.

[vii] Most patients take Pasireotide for 6 to 36 months after the initial trial period of 2 months as set out in the policy proposition.

[viii] Please see the Policy Proposition document for more detail. Average duration based on discussions with the policy working group.

[ix] Based on data extracted from the national IFR database.

[x] Based on data extracted from the national IFR database.

[xi] Based on discussions with the policy working group; Clinical Commissioning Policy (2014).

[xii] Please refer to the policy proposition.

[xiii] 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 2024/25. The growth rate that has been used accounts for Cushing's disease having a prevalence five times higher in women than in men: female population figures received a weight five times greater than that of men in calculating the growth rate. Figures are rounded.

[xiv] This uses the current incidence and growth of the population as set out in footnote xiii.

[xv] As the growth rate for the wider population is low, the number eligible for the treatment would be broadly constant in the next five.

[xvi] Based on discussions with the policy working group there would be no other changes to the pathway.

[xvii] This is based on an incidence of 1 to 2 per million as set out in K1.2. No specific drivers of growth or decline were identified. The growth in the number of patients accessing services is estimated to grow in line with demographic factors as set out in K1.6, and would be minimal.

[xviii] Most patients take the drug for an average duration of 6 to 36 months based on discussions with the policy working group.

[xix] The length of time for curative treatment to become effective is usually between 6 months and 3 years, but can last up to five (based on clinical input). An estimated 2/3 of patients could continue on after the initial trial which lasts two months. The range listed shows the position if there is response in 29% of patients for a low population (5 individuals per year), and a high response (67%) for a high population (10 patients per year). The patients in the year counts unique patients, regardless of the duration of treatment.

[xx] This is estimated to grow in line with the incidence of the population. The slow population growth, combined with the relatively low number of individuals affected by the disease, suggests a relatively constant activity level over time.

[xxi] Based on Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D. (March 2012), "A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease" in New England Journal of Medicine; 366: 914-924, , DOI: 10.1056/NEJMoa1105743, last accessed: 13/11/2015.

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

[xxiii] Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D. (March 2012), "A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease" in New England Journal of Medicine; 366: 914-924, DOI: 10.1056/NEJMoa1105743, last accessed: 13/11/2015.

[xxiv] Clinical Commissioning Policy, "Pasireotide for the treatment of Cushing's disease", March 2014 - NHS England A03/P/c

[xxv] Minniti, Giuseppe, & Brada, Michael. (2007). Radiotherapy and radiosurgery for Cushing's disease. *Arquivos Brasileiros de Endocrinologia & Metabologia*, *51*(8), 1373-1380. Retrieved November 18, 2015, from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302007000800024&lng=en&tlng=en.

[xxvi] This is based on a low case of 5 patients of which 29% are successful on pasireotide and receive 25 fractions, to 10 patients of which 67% respond and receive 28 fractions.

[xxvii] NHS England, (2013), Interim Clinical Commissioning Policy Statement: Stereotactic Radiosurgery /Radiotherapy for Ocular Melanoma and Pituitary Adenoma. [Online] accessed at: https://www.england.nhs.uk/wp-content/uploads/2013/09/d05-psa.pdf [Accessed: 17/11/15]. In an extract of SUS data in relation to Cushing' s disease from 2011/2012 to 2014/15 showed instances of fractionated rather than SRS as the primary OPCS codes (where the ICD-10 code E240 for pituitary dependant Cushing's disease is in the first three positions of the spell).

[xxviii] Losa M, Picozzi P, Redaelli M, G, Laurenzi A, Mortini P, Pituitary Radiotherapy for Cushing's Disease. Neuroendocrinology 2010; 92(suppl 1):107-110; and Minniti, Giuseppe, & Brada, Michael. (2007). Radiotherapy and radiosurgery for Cushing's disease. *Arquivos Brasileiros de Endocrinologia & Metabologia*, *51*(8), 1373-1380. Retrieved November 18, 2015, from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302007000800024&lng=en&tlng=en.

[xxix] Radiotherapy was reported as effective in around 73% (Minniti, Giuseppe, & Brada, Michael. (2007). Radiotherapy and radiosurgery for Cushing's disease. *Arquivos Brasileiros de Endocrinologia & Metabologia*, *51*(8), 1373-1380. Retrieved November 18, 2015, from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302007000800024&lng=en&tlng=en.) to 83% (Estrada et al. 1997 New England Journal of Medicine) of patients in a 3 -4 year horizon.

[xxx] Based on the estimate of 10 patients eligible per year, effectiveness of pasireotide at around 29%, and effectiveness of radiotherapy at around 73%.

[xxxi] North East Treatment Advisory group, "Pasireotide for Cushing's disease", NHS Regional Drug & Therapeutics Centre (Newcastle), June 2012. Discussion with the policy working group noted that the drug would be for a monthly prescription with follow up from the pharmacy (discussions held on 19/10/2015).

[xxxii] See K9

[xxxiii] NHS indicative price. Dictionary of medicine, http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=21207511000001101&toc=nofloat, last accessed: 09/11/2015.

[xxxiv] Based on discussions with NHS England pharmacists and finance leads.

[xxxv] See question above in relation to the delivery setting. The yearly cost is based on 2 doses of 900mcg per day at £108 (Dictionary of Medicine), and 20% VAT. If homecare arrangements were used, the VAT could be recoverable.

[xxxvi] Inclusion of the costs of two required appointments (at £93 each) for OP endocrinology and toxicity test (2014/15 Tariff). A 10% MFF has been applied. In addition, -1.6% (accounting for both inflation and the efficiency factor) has been applied to arrive at 2015/16 figures. The cost is therefore £101. Overall, the policy working group noted that it would be very difficult to say that there were more or less outpatient appointments in the new pathway as compared to the existing pathway.

[xxxvii] Based on the policy proposition.

[xxxviii] From 29% to 67% would be successful on the drug after 2 months as set out in K3.2.

[xxxix] The calculations underlying the figures shown in the appendix are set out below.

The cost of radiotherapy is estimated at £3,881. This is based on 25-28 fractions of external beam radiotherapy at £121 each (2014/15 tariff, HRG code SC23Z) and a one-off cost of £379 for planning (2014/15 tariff, HRG code SC45Z). A 10% MFF has been applied. In addition, -1.6% (for both inflation and efficiency) has been applied to arrive at 2015/16 figures.

There could be additional costs in relation to hyperglycaemia treatment (in around 46% of patients on pasireotide as noted in K 3.2). The cost of glucose-lowering drugs is £39 per month, per patient (assuming 2 metformin tablets of 850mg daily as first line treatment, as per discussions with the clinicians). This is based on a cost for 56 15mg/850mg Metformin tablets of £35.89 (Dictionary of Medicine). Hence the total yearly cost per patient is £468 for those affected (excluding VAT). This cost would not fall under specialised commissioning.

Additional costs could also be borne in relation to monitoring of cortisol levels (Clinical Commissioning Policy: pasireotide for the treatment of Cushing's disease. March 2014 - NHS ENGLAND A03/P/c.), to the extent these activities fall outside of the existing MDT and monitoring structure for the disease's management.

The cost of an adrenalectomy is estimated at £4,473. This has been calculated by using the 2014/15 tariff, which gives the cost of an elective adrenalectomy (£6,360) and a non-elective adrenalectomy (£4,052). These have been weighted by the proportion of elective and non-elective number of adrenalectomies in the latest HES dataset (2013/14). The weighted cost is £4,456. A 10% MFF has been applied. In addition, -1.6% (for both inflation and efficiency) has been applied to arrive at 2015/16 figures.

In addition, patients receive lifelong treatment of glucocorticoids and mineralocorticoids. The cost of these medications is estimated at a high level, at around £5,778 per year. (The cost of drugs is £18 per year, per patient. In addition, eight times a month patients undergo a therapy costing £60 per unit. This is based on discussions with the policy working group.) This cost has been taken as a proxy for the cost of lifelong medical treatment resulting from hypopituitarism after external beam radiotherapy.

[xl] Please see the policy proposition.

[xli] This could be 6 to 36 months, as set out in footnote vi.

[xlii] The policy working group noted that the time to respond to the therapy typically ranges between 6 months and 36 months.

[xliii] The supplementary protection certificate is not set to expire until after the 2025/26 fiscal year. Based on data provided from UKMi.

[xliv] Defined as the difference over the 'do nothing' scenario.

[xlv] The starting dose is indicated to be at least 600mcg per dose as per the previous commissioning policy. 300mcg would only be used if the trial is successful.

[xlvi] Note: the benefits of the policy in terms of reducing the number of adrenalectomies and associated lifelong drugs has been accounted for (see the Appendix for further detail).

[xlvii] Based on Colao (2012) – see footnote xxi

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