B05/S(HSS)/a

2013/14 NHS STANDARD CONTRACT

FOR PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA SERVICE (ADULTS AND ADOLESCENTS)

PARTICULARS, SCHEDULE 2 – THE SERVICES, A – SERVICE SPECIFICATION

Service Specification No.	B05/S(HSS)/a
Service	Paroxysmal nocturnal haemoglobinuria service (Adults and Adolescents)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

Paroxysmal nocturnal haemoglobinuria (PNH) is a very rare, acquired bone marrow disorder characterised by intravascular haemolysis with resultant anaemia often leading to transfusion dependence, severe disabling symptoms of haemolysis and, frequently, life threatening thrombosis.

There is convincing evidence that eculizumab is extremely effective in the treatment of haemolytic PNH. The initial pilot study of 11 patients clearly demonstrated that the intravascular haemolysis of PNH is stopped in all patients immediately after the initiation of eculizumab (Hillmen *et al,* 2004). The pilot study was performed solely in the United Kingdom with nine patients recruited in Leeds and two patients in London. The lactate dehydrogenase (LDH) is the most reliable marker of intravascular haemolysis and is usually at least ten times the upper limit of normal during an attack of haemoglobinuria. Even between attacks the LDH is usually markedly elevated. This immediate resolution of intravascular haemolysis leads to a dramatic reduction or complete resolution of many of the symptoms of the disease. There was a marked reduction in transfusion requirements with the monthly requirements falling from an average of 2.1 units of blood to 0.6 units of blood and over half of the patients becoming transfusion independent. There was also a significant improvement in quality of life as measured by the validated QLQ-C30 questionnaire and an almost complete resolution of haemoglobinuria in virtually all patients. The 11 patients from the pilot study were entered into an open-label extension trial (Hill *et al,* 2005).

After completion of the initial 12-week study, all patients chose to participate in the 52-week extension study. Eculizumab continued to be administered at 900 mg every 12 to 14 days, was sufficient to completely and consistently block complement activity in all patients. The reduction in haemolysis was maintained throughout the study, with a decrease in lactate dehydrogenase (LDH) levels from 3110.7 international units per litre (IU/L) before treatment to 622.4 IU/L ($P < 0.002$). The proportion of PNH type III RBCs increased from 36.7% at baseline to 58.4% ($P < 0.005$). The paroxysm rate of days with gross evidence of haemoglobinuria per patient each month decreased from 3.0 during screening (before the Pilot study) to 0.2 ($P < 0.001$) during treatment. The median transfusion rate decreased from 1.8 U per patient each month before eculizumab treatment to 0.3 U per patient each month ($P <0.001$) during treatment. Statistically significant improvements in quality-of-life measures were also maintained during the extension study. Eculizumab continued to be safe and well tolerated, and all patients completed the study. The close relationship between sustained terminal complement inhibition, haemolysis, and symptoms was demonstrated. Eleven patients were treated in the initial pilot study and 9 of these patients remain on eculizumab in excess of 8 years since commencing therapy with continued benefit from treatment. One patient stopped eculizumab as her disease was predominantly aplastic anaemia, rather than haemolytic PNH, and she remains transfusion dependent. The other patient stopped eculizumab because his PNH clone fell to less than 10% and eculizumab was no longer required. He remains well after stopping eculizumab in early 2009.

The pilot study then led to two further trials the first of which, the TRIUMPH study, was a randomised double blind placebo controlled trial of eculizumab and the open-label SHEPHERD study, in which 97 patients were treated with eculizumab and this group of patients allowed the treatment of patients with less heavy transfusion requirements and with a lower platelet count (>30 x 10^9/l). Both the TRIUMPH and the SHEPHERD studies recruited a large number of patients from the United Kingdom.

The TRIUMPH study (Hillmen *et al.* 2006) was a double-blind, randomized, placebo-controlled, multi-centre, phase III trial. Patients had to be transfusion dependent (defined as requiring at least four transfusions in the last 12 months) and to have a platelet count in excess of 100 x 10^9/l. The patients were randomized to receive either placebo or eculizumab intravenously; eculizumab was given at a dose of 600 mg weekly for four weeks, followed one week later by a 900-mg dose and then 900 mg every other week through week 26. The two primary end points were the stabilization of haemoglobin levels and the number of units of packed red cells transfused. Biochemical indicators of intravascular haemolysis and the patients' quality of life were also assessed. Eighty-seven patients underwent randomization. Stabilization of haemoglobin levels in the absence of transfusions was achieved in 49% (21 of 43) of the patients assigned to eculizumab and none (0 of 44) of those assigned to placebo (P<0.001). During the study, a median of 0 units of packed red cells was administered in the eculizumab group, as compared with 10 units in the placebo group (P<0.001). Eculizumab reduced intravascular haemolysis, as shown by the 85.8% lower median area under the curve for lactate dehydrogenase plotted against time (in days) in the eculizumab group, as

compared with the placebo group (58,587 vs. 411,822 U per liter; P<0.001). Clinically significant improvements were also found in the quality of life, as measured by scores on the functional assessment of chronic illness therapy-fatigue instrument (P<0.001) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. Of the 87 patients, 4 in the eculizumab group and 9 in the placebo group had serious adverse events, none of which were considered to be treatment-related; all these patients recovered without sequelae. The patients from the TRIUMPH study were eligible to enter a further study (the extension study) in which all patients continued to received eculizumab, This meant that the placebo patients were eligible to receive eculizumab after they had completed 6 months of follow-up in the TRIUMPH study.

In the SHEPHERD study (Brodsky *et al,* 2008) eculizumab treatment was extended in an open-label, non–placebo controlled, 52-week, phase III trial assessing both the safety and efficacy of eculizumab in a broader population of patients with PNH. Eculizumab was administered in the same dose schedule as in the TRIUMPH and pilot studies for a total treatment period of 52 weeks. Ninety-seven patients at 33 international sites were enrolled. Patients treated with eculizumab responded with an 87% reduction in haemolysis, as measured by lactate dehydrogenase levels (P < 0.001). Baseline fatigue scores in the FACIT-Fatigue instrument improved by 12.2 +/- 1.1 points (P < 0.001). Eculizumab treatment led to an improvement in anaemia. The increase in haemoglobin level occurred despite a reduction in transfusion requirements from a median of 8.0 units of packed red cells per patient before treatment to 0.0 units per patient during the study (P < 0.001). Overall, transfusions were reduced 52% from a mean of 12.3 to 5.9 units of packed red cells per patient. Forty-nine patients (51%) achieved transfusion independence for the entire 52-week period. Improvements in haemolysis, fatigue, and transfusion requirements with eculizumab were independent of baseline levels of haemolysis and degree of thrombocytopenia. Quality of life measures were also broadly improved with eculizumab treatment. This study demonstrated that the beneficial effects of eculizumab treatment in patients with PNH were applicable to a broader population of PNH patients than previously studied.

The role of eculizumab in preventing and treating the thrombotic complications of PNH was reported in 2007 (Hillmen *et al,* 2007). The thrombosis in PNH patients is the principle cause of premature mortality and is probably multi-factorial in causation with roles postulated directly due to the intense intravascular haemolysis and the unopposed action of activated complement on PNH platelets. These possible causes are both dependent on complement activity and therefore it might be expected that eculizumab would have a major impact on thrombotic complications. The impact of eculizumab on the thromboses in PNH was addressed by combining the data from the pilot TRIUMPH, SHEPHERD and extension studies in order to have enough patients treated with eculizumab to be meaningful. A total of 195 patients were entered into these studies and continued treatment in a multi-national open-label extension study. Thromboembolism (TE) rate with eculizumab treatment was compared with the pretreatment rate in the same patients. The TE event rate with eculizumab treatment was 1.07 events/100 patient-years compared with 7.37 events/100 patient-years (*P* < 0.001) prior to

eculizumab treatment (relative reduction, 85%; absolute reduction, 6.3 TE events/100 patient-years). With equalization of the duration of exposure before and during treatment for each patient, TE events were reduced from 39 events before eculizumab to three events during eculizumab ($P < 0.001$). The TE event rate in antithrombotic-treated patients (n = 103) was reduced from 10.61 to 0.62 events/100 patient-years with eculizumab treatment ($P < 0.001$). These results show that eculizumab treatment reduces the risk of clinical thromboembolism in patients with PNH.

Renal failure is extremely common in PNH and has been reported to contribute to between 8% and 18% of the deaths due to the disease. Renal damage in PNH is associated with chronic haemosiderosis and/or microvascular thrombosis. The incidence of renal dysfunction or damage, as defined by stages of chronic kidney disease (CKD), in the cohort of 195 patients with PNH entered in the pilot study, TRIUMPH and SHEPHERD was recently reported. Also the safety and efficacy of the complement inhibitor eculizumab in altering its progression was evaluated in the same paper (Hillmen *et al,* 2010). Renal dysfunction or damage was observed in 65% of the study population at baseline with 21% of patients with later stage Chronic kidney disease (CKD) or kidney failure (GFR ≤ 60 mL/min/1.73 m^2; stage 3, 4 or 5). Eculizumab treatment was safe and well-tolerated in patients with renal dysfunction or damage and resulted in the likelihood of improvement as defined as categorical reduction in CKD stage (P<0.001) compared to baseline and to placebo (P=0.04). Improvement in renal function during eculizumab treatment was more commonly seen in patients with baseline CKD stage 1-2 (67.1% improvement, P<0.001) although improvement was also observed in patients with CKD stage 3-4 (P=0.05). Improvements in renal function occurred quickly and were sustained for at least 18 months of treatment. Patients that were categorized at CKD stage 3-5 did not worsen during treatment with eculizumab. Overall, 40 (21%) of 195 patients that demonstrated renal dysfunction or damage at baseline were no longer classified as such after 18 months of treatment. Administration of eculizumab to patients with renal dysfunction or damage was well tolerated and was usually associated with clinical improvement.

In PNH pregnancy is associated with increased maternal and foetal complications to such an extent that pregnancy has been considered relatively contra-indicated in PNH. We have recently reported on seven patients exposed to eculizumab at different stages of pregnancy including the first two patients to receive the drug from conception to delivery (Kelly *et al*, 2010). In these patients and an additional case reported subsequently (Marasca *et al,* 2010) eculizumab appears to be safe to use in treating pregnant patients with PNH. There appears to be little or no passage of eculizumab across the placenta or into breast milk. Many more patients need to be described to ensure that the complications of pregnancy are prevented by eculizumab but the early information suggests that this is the case.

2. Scope

2.1 Aims and objectives of service

The aim of the national PNH service for paroxysmal nocturnal haemoglobinuria (PNH) is to care for and support patients with PNH from throughout England and by agreement with the rest of the United Kingdom. There is an agreement in place with the healthcare commissioners in Scotland, but separate funding arrangements need to be put in place by healthcare providers for Wales and Northern Ireland for the national PNH service to provide support to patients with PNH in those countries. The population of patients includes all patients diagnosed with a PNH clone in the United Kingdom. The service will assess patients and recommend the most appropriate treatment for each individual. Most therapies, primarily those delivered locally, such as transfusions, erythropoietin, iron chelation and immune suppression therapies will be delivered by the local haematology service and are not funded by NHS England. However the management of patients who are receiving eculizumab, anti-complement targeted therapy for PNH, will be the responsibility of the national PNH service.

The national PNH service developed following the successful clinical trials of a novel therapy for haemolytic PNH, namely eculizumab or Soliris. The initial trial of eculizumab only recruited patients from the United Kingdom. The two subsequent eculizumab trials, including the placebo-controlled TRIUMPH study, were undertaken and the UK was again the largest recruiter of patients worldwide. Eculizumab is a life-changing therapy in haemolytic PNH which is effective in almost all such patients and was therefore commissioned through NHS England in 2008.

The aim of the national PNH service is to provide an exceptional service to ensure the highest quality management of patients with PNH. It is desirable that patients with PNH should have their treatment delivered as close to their homes with little disruption to their lifestyle, as treatment with eculizumab will be a life-long therapy for many patients, and to ensure that patients have equal access to treatment regardless of where they live in the United Kingdom or of their socio-economic circumstances. The PNH service aims to review all patients with PNH and will support local haematologists in their management. It is important that the national PNH service reviews not only patients requiring eculizumab but also other patients as they may have complex management decisions to make. The prevention of complications is a critical part of their optimal management and although patients may not require therapy at presentation this can change with evolution of their illness. As well as reviewing all patients with PNH, the service is responsible for the appropriate selection of patients who may benefit from eculizumab therapy to ensure that the selection of patients is consistent nationwide. This will ensure that all patients with PNH have equal access to effective therapy but also that there is a cost-effective, auditable use of this expensive therapy. It will also be possible to maintain the education of patients, their carers and healthcare personnel involved in their care to effectively manage any complications of PNH and its therapy.

Therefore there is an important educational role of the national PNH service. The service manages the prescriptions, delivery and all aspects of the management of patients on eculizumab for PNH.

The objective of the service is to provide comprehensive management for all patients with PNH in England and by agreement with the rest of the United Kingdom. This includes all aspects of the management of patients on eculizumab including the decision regarding which patients will benefit from therapy (using criteria agreed with NHS England), the prescription and management of eculizumab therapy including the management of homecare treatment. In addition the service will provide advice and assist in the management of all patients with PNH in England and by agreement with
the rest of the United Kingdom. An important role of the service is the continued education of all professionals involved in the care of patients with PNH. The national PNH service aims to provide a service available to all patients in England and by agreement with the rest of the United Kingdom with equal access regardless of where patients live.

The clinical outcomes that will be measured are:

- the impact of eculizumab and the PNH service on patients and their carers including measures of effectiveness of eculizumab in our population
- the continued reduction of transfusion requirements compared to prior to therapy
- improvements in quality of life (as assessed by Global PNH Registry questionnaire
- protection against thrombotic complications
- avoidance and management of the side effects of eculizumab, specifically occurrence and management of meningococcal infection

In addition survival of patients on therapy will be collected. Patient questionnaires regarding the effectiveness of the PNH Service will be regularly performed.

Routine measures of performance will be assessed including:

- waiting times for initial visit
- transfusion frequency
- unplanned admissions
- rate of thrombosis and meningococcal infections
- the numbers of patients on eculizumab
- wastage
- the number of patients stopping eculizumab

2.2 Service description/care pathway

Paroxysmal nocturnal haemoglobinuria (PNH) is a very rare, acquired bone marrow disorder characterised by intravascular haemolysis with resultant anaemia often leading to transfusion dependence, severe disabling symptoms of haemolysis and,

frequently, life threatening thrombosis. PNH arises due to an acquired somatic mutation of the phosphatidyl inositol glycan complementation group A (*pig-a*) gene in a haematopoietic stem cell which results in a haematopoietic clone that is deficient in a number of cell surface antigens. (Hill *et al.,* 2007a) These antigens are usually attached to the cell surface by a particular form of link, called a glycosyl-phosphatidyl-inositol (GPI) anchor. The *pig-a* gene is a critical gene in the biosynthesis of GPI structures which explains the GPI deficiency in PNH. The PNH clone appears to remain under normal control of haematopoiesis in that it does not appear to have a malignant potential, differentiates down all haematopoietic lineages including all myeloid compartments (neutrophils, monocytes, platelets, etc.) and lymphocyte subsets (both T and B-cells). In fact it appears that there is an appropriate neutrophil response from the PNH clone when patients experience infections and also a response in erythropoiesis to exogenous erythropoietin. Therefore the PNH clone is under normal haematopoietic control but is "weaker" than normal haematopoiesis as the cells are deficient in a number of cell surface antigens, for example including the complement regulatory proteins CD55 (decay accelerating factor) and CD59 (membrane inhibitor of reactive lysis) which renders the clone extremely sensitive to lysis by activated complement.

It might be considered counterintuitive that a weak clone such as PNH can expand to dominate haematopoiesis in patients as many have over 95% or even 100% of their haematopoiesis derived from the PNH clone. In addition there is evidence that everyone develops PNH clones but that these usually remain at extremely low levels (less than one PNH stem cell in 100,000 normal stem cells) without expanding. This anomaly is explained by the association of PNH with bone marrow failure syndromes, particularly immune-mediated aplastic anaemia as approximately a third of patients with PNH have previously diagnosed aplastic anaemia and the other two-thirds have some evidence of an underlying bone marrow failure. There is increasing evidence of a defect in the stem cell pool in PNH patients (Elebute et al, 2003) and of an overlap in the haemopoietic defect in aplastic anaemia and PNH (Marsh and Elebute, 2003). Aplastic anaemia in itself is rare (approximately 1 case in 100,000 population) indicating that the association between aplastic anaemia and PNH cannot be a chance finding. The overwhelming evidence is that aplastic anaemia is due to an auto-immune attack on normal haematopoietic stem cells and that PNH cells, presumably due to their deficiency in Glycosylphosphatidylinositol (GPI)-linked antigens, are relatively spared from this assault. Therefore PNH stem cells have a relative growth advantage over normal stem cells in the setting of immune-mediated aplastic anaemia or other bone marrow failure explaining their expansion and domination of haematopoietic activity in many patients. However the deficiency of certain GPI-linked antigens, particularly CD59, renders the PNH cells sensitive to activated complement, leading to severe and continuous intravascular haemolysis and all of the symptoms and complications of the disease.

PNH is a chronic disease often affecting young adults (although it is seen in all ages) which usually persists for the remainder of the patient's life and results in the death of approximately half of sufferers. There is a wide spectrum of clinical phenotypes in PNH ranging from almost entirely asymptomatic with a normal, or

near normal, blood count to patients with severe disabling intravascular haemolysis, characterised by recurrent episodes of passing red or black urine due to haemoglobinuria (paroxysms) during which patients often have profound symptoms including any or all of the following:

- severe abdominal pain (occasionally requiring high doses of opiates)
- borgorrymia (abdominal bloating)
- dysphagia, which is often painful, with some patients being unable to swallow even fluid at times
- profound lethargy out-of-keeping with the degree of anaemia which is due to the direct effects of intravascular free haemoglobin and nitric oxide depletion
- men suffer from erectile failure which can be absolute and continuous

The symptoms may be continuous. The exacerbations, or paroxysms, often last for four to seven days and may be triggered by relatively trivial infections or be spontaneous and in some patients can be almost continuous. For reasons that remain unclear the haemoglobinuria is usually worse in the mornings and clears through the day (hence the term “nocturnal”). The continuous intravascular haemolysis leads to anaemia in most patients and may require regular transfusion support. The disease is chronic with only a minority of patients experiencing a spontaneous remission (Hillmen *et al.*, NEJM 1995), occurring 10 to 20 years after the initial diagnosis and most patients having the disease from diagnosis (median age at diagnosis is 39 years [range: 8 to 88 years]; Hill *et al.*, 2007b) for the remainder of their life. The reason why patients have different severities of disease is due in part to the size of the PNH clone – some patients have relatively small PNH clones (for example less than 10% PNH neutrophils) usually in the context of aplastic anaemia and in these patients the predominant clinical features are those of the underlying bone marrow failure rather than uncontrolled effects of activated complement and haemolysis. These patients with predominantly bone marrow failure rarely benefit from eculizumab therapy. However there are other patients with large PNH clones, usually over 40% PNH neutrophils, who frequently have predominantly haemolytic and thrombotic disease. Even in patients with very large clones the severity of symptoms, anaemia, occurrence of thrombosis and the dependence on transfusions, varies greatly between patients. The reason for this variation is unclear at present but does mean that only a proportion of patients with haemolytic PNH will be severely enough affected to require eculizumab. These variations in the disease phenotype are part of the reason that the management of patients with PNH can be complex and justify the development of the national PNH service.

The most common complication of PNH is venous or arterial thrombosis (Hall *et al.,* Blood 2004). The venous thrombosis in PNH has a predilection for unusual sites such as the hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins such as the mesenteric or renal veins, and cerebral veins. In addition, there is an apparent increased risk of arterial thrombosis, either cerebro-vascular accidents or myocardial infarctions at an early age. Thrombosis occurs in approximately half of patients with haemolytic PNH and is the cause of death in a third of patients. Approximately 10% of patients present with thrombosis as the first manifestation of their PNH. The occurrence of a patient’s first thrombosis is a sinister development as many patients continue to have further thromboses despite anticoagulation and eventually succumb from thrombotic complications – this “spiral” of thromboses is a classic feature of PNH. The relative risk of a patient dying after they develop their first thrombosis is 10-fold higher than patients who don’t develop this complication (de Latour *et al.*, Blood 2008). Eculizumab is effective at preventing further thrombosis in a patient with PNH and is a very important therapy in PNH when

patients suffer such complications.

PNH is the disorder with the most profound chronic intravascular haemolysis. This is a result of the deficiency of the PNH red cells of complement regulatory molecules, mainly the membrane inhibitor of reactive lysis (MIRL or CD59) which is the principle regulator of terminal complement. The best routine measure of the degree of intravascular haemolysis is the level of lactate dehydrogenase (LDH) which in PNH is usually at least 10 times above the upper limit of normal during an attack of haemoglobinuria. This degree of haemolysis results in the release of free haemoglobin into the plasma and the subsequent depletion of nitric oxide (NO). (Rother *et al.*, 2005; Hill *et al.*, 2010) NO is a critical molecule in several homeostatic functions and its depletion results in the abnormal contraction of smooth muscle. This seems to be the reason why patients suffer spasm of the gastrointestinal tract and this results in the dysphagia, abdominal pain and borborygmus. In addition smooth muscle dysfunction is probably responsible for the erectile failure seen in PNH. It also seems that the depletion of NO is the cause of the severe lethargy seen in PNH. Some of the complications of PNH, such as stricture of segments of the small bowel, pulmonary hypertension and possibly thrombosis are contributed to by NO depletion. In addition other complications result from the chronic intravascular haemolysis including:

- iron loading of the renal tubules and the subsequent chronic renal failure which is observed in over half of patients with PNH which may lead to dialysis dependency and
- cholelithiasis (gall-stone disease) which is extremely common in PNH. During episodes of brisk haemolysis (the paroxysms) occasionally patients may suffer acute renal failure requiring renal dialysis usually for a short period of time

Severe symptomatic anaemia is common in patients with PNH. Many patients become transfusion dependent and may remain dependent of transfusions for many years or even decades. As patients tend to lose iron in their urine they do not become iron overloaded as most other patients who are transfusion dependent for other reasons, such as thalassaemia become and therefore patients with PNH have been able to withstand huge quantities of transfused units of blood without developing life threatening complications of iron toxicity. Many patients with PNH will have received several hundred transfusions over a prolonged period of time. This can result in patients developing multiple antibodies to red cell antigens meaning that identifying suitable blood for transfusion can be demanding and therefore expensive.

Pregnancy is a particular high risk time for women with PNH. There is a very high risk of maternal complications during pregnancy and in the immediate post partum period. The greatest risk is that of thrombosis which can lead to death. The reported maternal mortality in PNH is between 12% and 21%. (Ray *et al*, 2000; Fieni *et al*, 2006) There is also a risk of developing a relapse of bone marrow failure (aplastic anaemia) during pregnancy which can be extremely difficult to treat. There is no apparent increased risk of congenital abnormalities in the babies born to PNH mothers (PNH is an acquired, not inherited, genetic condition) but there is an increased risk of prematurity and miscarriages due to maternal complications. It appears that many of the complications of PNH are largely

prevented by the use of eculizumab during pregnancy. (Kelly *et al.*, 2010a)

The diagnosis of PNH is established by flow cytometry immunophenotyping, a highly specialised technique that is performed in specialist laboratories by expert scientific staff. (Richards *et al.,* 2007) Although many screening tests for PNH are carried out to exclude the diagnosis, it is important when new cases are identified that results are interpreted appropriately and communicated to the referring clinician as soon as possible.

The Haematological Malignancy Diagnostic Service (HMDS) laboratory in Leeds is at the forefront of technical developments in PNH screening and has investigated over 500 patients with PNH over the last 15 years. Not only is the initial diagnosis of PNH important, but the subsequent follow-up measurement of patients' PNH clone sizes can directly affect patient management and predict clinical course. The results of PNH testing by flow cytometry give an indication of disease activity at the stem cell level. Furthermore, the continued follow-up of patients on eculizumab therapy is essential to monitor the effectiveness of treatment. Continued and regular follow-up of all PNH patients is important for identifying those patients who may progress from aplastic anaemia/other bone marrow failure syndrome to haemolytic PNH, those with stable disease and those who undergo spontaneous recovery. Changes in clone size are not rapid, and in the case of spontaneous recovery may take months to years but can offer encouraging news for patients with this long term illness. Another important aspect of monitoring patients by flow cytometry is the ability to detect those rare patients that progress to acute myeloid leukaemia.

Historically approximately 50% of patients with PNH died due to complications of PNH (Hillmen *et al.*, 1995). In historical series the median survival was 10 years from diagnosis with 25% of patients surviving 25 years compared to 78% for an age-matched control population. Most of these patients died as a result of thrombosis. It is likely that the median survival improved with modern supportive care, such as better anticoagulation therapy, thrombolysis, renal dialysis and bone marrow transplantation, to around 15 years from diagnosis however it is clear that patients still died of the complications of PNH.

The development of anti-complement therapy with the monoclonal antibody eculizumab has had a profound impact on the management of haemolytic PNH with a marked effect on the complications of the disease including the prevention and treatment of thrombosis and on renal dysfunction. There is now good evidence from the follow-up of patients remaining on treatment for in excess of eight years that eculizumab has a profound impact on the survival of patients with PNH. (Kelly *et al.*, 2010b) The survival of patients on eculizumab appears to be similar to that of age-matched control subjects from the normal population.

The management of PNH was largely supportive until the advent of eculizumab (soliris) which was approved for the use in PNH in Europe in June 2007. Bone

marrow transplantation remains the only potentially curative treatment for PNH but the transplant-related mortality is reported to be approximately 44%, which is

widely considered too high to justify the use of allogenic stem cell transplantation except for in very selected individuals, for example those patients with syngeneic twins. (Saso *et al*., 1999) Spontaneous remissions are reported in PNH and a study looking at the long-term follow-up of patients with PNH reported that 12 of 80 patients experienced a spontaneous remission of their disease between 10 and 20 years after the initial diagnosis. In fact a third of patients who survived 10 years in this series had a spontaneous remission.

Eculizumab therapy has revolutionized the management of PNH. Patients on eculizumab therapy are usually asymptomatic, or at the very least have a marked improvement in symptoms, are frequently rendered transfusion independent (two thirds of patients at the Leeds Service; Kelly *et al.*, 2010b and about half of patients at the King's College Hospital NHS Foundation Trust service in London; Kulasekararaj *et al* 2010) and are able to begin to function normally in their work and family commitments. Eculizumab also prevents the development of and propagation of thrombosis thus having a major impact on the serious morbidity and the principal cause of mortality in PNH. Eculizumab has no effect on the bone marrow failure component of PNH.

The national PNH service is delivered by centres at Leeds Teaching Hospitals NHS Trust and King's College Hospital NHS Foundation Trust, London with referrals being recommended on a geographical basis with King's receiving referrals from London and the South East and Leeds receiving referrals from the remainder of the United Kingdom. Patients are referred to one of the two centres by the patient's local haematologist, usually by geographical location but also by patient choice.

The national PNH service is responsible for the selection of patients who fulfil the approved criteria for treatment with targeted therapy for PNH, namely eculizumab (appendix 2). The national PNH service will ensure the appropriate management of patients with PNH on eculizumab including the appropriate prevention and management of meningococcal infection. The PNH service is responsible for the prescription of eculizumab and the delivery of therapy either initially in the hospital or after the first 2 to 5 infusions at home utilising a homecare provider (currently Healthcare-at-Home). The national PNH centre is responsible for overseeing home delivery of therapy and the education of the homecare nurses to ensure the safe administration of therapy, as well as providing information in respect of the disease. The national PNH service is responsible for the ongoing management of patients on eculizumab therapy and for continuing to advise the local haematologist on the appropriate management of all aspects of PNH.

Service model and Care Pathways

The national PNH service is based on a model which ensures that the patient journey is the same at each commissioned centre. Patients are evaluated in clinic, monitored for organ damage and complications relating to PNH and, where appropriate, prescribed eculizumab alongside other therapies. The prescriptions of eculizumab and subsequent management of these patients is undertaken by the PNH service. The patient remains under the care of their local haematology department also in a shared care format. This is important because if an acute complication arose in a patient they would be admitted locally. For patients who are

to commence eculizumab, at least the first and second infusions are usually delivered in the PNH centre. The maintenance dose of the drug requires intravenous administration every 2 weeks, usually indefinitely for the majority of patients. To allow convenient access to long-term treatment, eculizumab is then delivered and administered in the patients' homes. The infusions are delivered by homecare nurses who are educated in the administration of eculizumab by the PNH team. An electronic report is forwarded to the PNH nurse specialist at the prescribing site within 48 hours post infusion to update them of any problems the patient is suffering and the PNH nurses will follow-up with the patient as appropriate and discuss with the consultants in the PNH service as defined.

Patients receiving eculizumab are seen at least every 12 weeks in the PNH service outpatient clinic and other patients with PNH not on eculizumab are seen as necessary. The clinical nurse specialists also support the patients and their families in between clinic appointments with frequent telephone consultations. As well as outpatient advice, if a patient was admitted to their local hospital, advice on continued management is provided with regular interaction with the local teams.

Patients who give consent are also enrolled in the Global PNH Registry, which is an anonymised international study. The providers have access to the data on patients in the United Kingdom with the aim of monitoring the progression of the disease, as well as capture quality of life data and safety and effectiveness data of eculizumab.

The service provides a 24 hour, 7 days a week on-call service with patients having direct access to a PNH specialist consultant and/or a haematology consultant (depending on location) for advice relating to the disease or therapy, particularly to ensure rapid and appropriate management of complications including acute thrombosis and meningococcal septicaemia which is a recognised risk in patients receiving eculizumab.

The laboratory diagnosis and follow-up of PNH, which requires specific expertise, is made at both the haematological malignancy diagnostic service (HMDS) in Leeds Teaching Hospitals NHS Trust and the haematology malignancy diagnostic centre (HMDC) at King's College Hospital NHS Foundation Trust, using the same flow cytometric technology that is considered the gold standard for testing.

The providers will work with the service commissioners to ensure sufficient considerations are given to communications with patients and interested parties. To this end the service is currently developing a website designed to ensure that appropriate and up-to-date information is communicated to patients regularly. Comprehensive patient information leaflets on PNH with input from patients and their carers have also been produced, which has significantly improved the understanding of patients about their condition, possible complications and available treatment. An information leaflet has also been developed for patients on eculizumab who wish to travel abroad. The leaflet outlines precautions that should be taken and the process to facilitate patients receiving an occasional infusion at their travel destination if this is deemed to be appropriate.

Patient surveys are undertaken regularly in order to ensure the delivery of the

service meets with their requirements and will enable improvements and development. These surveys often are general audits of the service but occasionally targeted patient communications are undertaken to address specific questions, such as the proposal to set up a new outreach clinic. A patient group, which includes their relatives, has also been developed and are encouraged and supported to meet regularly. This group has been meeting for the last three years and is supported by both centres.

High quality governance is recognised as being essential to ensure the appropriate delivery of the national PNH service objectives and to ensure continued development of the service. At both centres there is a weekly meeting where patient specific issues are discussed, as are the organisation of the activity of the service including future outreach clinics, educational activities, etc. In addition, the senior members of the team meet regularly to discuss the development of the PNH service. There is a responsibility to educate and develop knowledge in the area of PNH both nationally and internationally. This also enables a dissemination of information regarding the nationally commissioned PNH service with an encouragement to refer appropriate patients. This is achieved with regular lectures and meetings. In order to maintain a high quality standardised service, there are regular communications across the centres, local multi-disciplinary team meetings (MDTs), audit and assessments of current practice.

In addition, there are regular joint meetings between the national commissioners and the clinical teams from the centres to facilitate clinical governance.

Patients are diagnosed with PNH almost always by the local haematology service in their area. The patient is then referred into one of the PNH- designated centres depending on where they live. Patients from London and the Home Counties are referred to King's College Hospital NHS Foundation Trust and patients from elsewhere are referred to the service at Leeds Teaching Hospitals NHS Trust. Patients referred to the Leeds service are reviewed in the PNH clinic either in Leeds or one of the outreach clinics (Southampton, Bristol, Birmingham, Oxford, Peterborough or Lanarkshire). Patients are assessed to decide what therapy they should receive including, but not restricted to, whether they should receive eculizumab. Patients who do not require eculizumab are referred back to the referring centre with recommendation regarding their treatment which is delivered by the local haematology service. These patients are reviewed in the PNH clinic as appropriate.

Patients who require eculizumab are counselled regarding therapy and have the necessary vaccination prior to commencing. As well as vaccination against *Neisseria meningitidis,* antibiotic prophylaxis is given to all patients (penicillin V 500mg twice a day or erythromycin 500 mg twice a day for patients intolerant of penicillin). Annual monitoring of patients' level of immunity is carried out with samples sent to the Health Protection Agency laboratory in Manchester.

The initial 2 to 5 eculizumab infusions are given in the PNH centre and subsequent infusions are given at home. A referral for treatment at home is made at initiation of therapy and the patient is reviewed by the homecare team at the PNH centre during one of the first 5 infusions to discuss the home treatment. Patients are then

administered eculizumab at home every two weeks. The prescriptions are managed by the PNH service and patients are reviewed in the PNH clinic at least every 12 weeks.

Links are made to other services as appropriate. For example when patients with PNH are pregnant there is a close interaction with the obstetric haematology service in order to manage the pregnancy optimally. In patients with liver complications patients are managed together with the nationally commissioned local hepato-biliary service. Services that are provided locally are funded locally.

Days/hours of operation

The PNH service operates clinics during working hours. Eculizumab is generally also given during working hours although with agreement with the homecare team this may also occur in the early evenings or Saturday mornings to accommodate an individual patient's requirements. The PNH service operates a 24-hour/day, 7-day on-call service in which one of the PNH consultants and/or a consultant haematologist is always available. Patients are instructed to call if they are unwell, particularly if they have any symptoms suggestive of meningococcal infection (the principle concern for patients receiving eculizumab).

Referral criteria, sources and routes

Most patients will be referred to the PNH service by their local haematology team. Occasionally there may be referrals from alternative healthcare professionals such as the patient's general practitioner (GP). In these instances a member of the PNH team will discuss the referral with the local haematology team prior to the patient being seen within the service.

Referrals are reviewed by a consultant in the PNH service prior to being seen and are allocated to a clinic depending on both the geographical location the patient resides and the clinical urgency for the patient to be seen.

A blood sample is requested on patients to evaluate the proportion of PNH cells present in the blood. This sample is sent to one of the designated PNH centres so that when the patient is reviewed an accurate level is available to the PNH team.

Discharge criteria & planning including any transition arrangements

The care of patients with PNH is shared between the national PNH centre and the local haematology unit. The PNH centre is responsible for the management of all aspects of eculizumab. The delivery of other care remains the responsibility of the local haematology unit. The PNH centre liaises closely with the local unit often by telephone regarding the care of patients.

The national service will be responsible for:

- advice on the treatment of PNH including patient eligibility for eculizumab
- funding, prescription and delivery of eculizumab including eculizumab administration at the patient's home
- regular review of patients, including 12 weekly reviews of patients on

eculizumab
- a 24 hour PNH on-call service to allow direct access to specialist advice for patients and healthcare professional
- PNH laboratory testing for patients within the PNH service

A close liaison between the national PNH team and local haematology teams should be maintained to optimise patient care with the local haematology units being responsible for:
- referral of patients to the PNH service
- “routine” care such as transfusions
- management of complications of PNH with liaison with the designated PNH centre
- prescription and funding of non-eculizumab therapies (i.e. warfarin, ciclosporin, erythropoietin, iron chelation therapies)

Patients with PNH will be followed up through lifelong monitoring to ensure their disease and clone sizes are monitored regularly and the appropriate treatment is provided. In the rare occurrence of spontaneous remission the patient will be offered continued annual follow-up in the PNH service to maintain their involvement in the PNH Registry and ensure no late sequelae of PNH, such as recurrence of aplastic anaemia. Patients undergoing successful stem cell transplantation may be discharged from the service as they will be followed by the local bone marrow transplant service.

2.3 Population covered

The national PNH service receives referrals from throughout the United Kingdom. The centre at Leeds Teaching Hospitals NHS Trust is responsible for patients in Hampshire, Oxfordshire, Wiltshire, Northamptonshire, Cambridgeshire, Suffolk, East Anglia, South West, the Midlands and the North. In addition the Leeds PNH centre, at the Leeds Teaching Hospital NHS Trust, looks after patients from Scotland (seen in the Lanarkshire clinic), Wales (seen either in Bristol or Leeds) and Northern Ireland (seen in Leeds).

The centre at Kings College Hospital NHS Foundation Trust is responsible for patients in Greater London and the Home Counties (Bedfordshire,

Buckinghamshire, Sussex, Essex, Hertfordshire, Kent, Surrey and Berkshire).

Patients also have the right to choose a centre or outreach clinic location independent of geography.

2.4 Any acceptance and exclusion criteria

PNH occurs at an equal rate in males and females and can present at any age, from childhood to the elderly. Paediatric patients are seen by one of the PNH

consultants in an age appropriate environment within the Department of Paediatric Haematology with the appropriate paediatric qualified nursing support at hand. The model of the national PNH service is to take the patient's treatment and follow-up as close to home as possible. To this end, all of the eculizumab infusions, after the initial 2 to 5, are given in the patients' homes. In addition the outreach clinics mean that local patients can largely be seen in their own local areas, therefore ensuring equality of access to the service independent of income or social class. The national PNH service has a duty to co-operate with the commissioner in undertaking equality impact assessments as a requirement of race, gender, sexual orientation, religion and disability equality legislation.

All patients referred to the PNH service will be offered an appointment either at one of the two designated PNH centres or at one of the PNH outreach clinics, depending on the geographical location of the referred patient. All patients referred will be offered an outpatient appointment within 4 weeks of the referral being received by the PNH team. This initial appointment may be delayed if the patient is keen to attend a specific outreach clinic rather than be seen within four weeks at one of the designated PNH centres.

Patients who are symptomatic and likely to be eligible for treatment with eculizumab will be seen urgently within two weeks of the referral being received.

Patients who are referred to the PNH service but who after analysis by flow cytometry at either designated PNH centre are found not to have PNH will be excluded from the national PNH service.

2.5 Interdependencies with other services

The providers of the nationally commissioned PNH service include:

- Leeds Teaching Hospitals NHS Trust
- King's College Hospital NHS Foundation Trust
- Alexion Pharmaceuticals Inc
- Healthcare-at-Home Ltd

The whole clinical service is delivered by the two NHS hospital trusts. Alexion fully funds the delivery and administration of eculizumab which is then carried out by Healthcare-at-Home. They have also undertaken to replace any wastage incurred with the Homecare service.

Outreach clinics currently occur in Birmingham, Oxford, Bristol, Southampton, Peterborough or Lanarkshire, Scotland, and negotiations are currently underway to set up outreach clinics in London to be based at Imperial College Healthcare NHS Trust and St George's Healthcare NHS Trust. Each member of staff who travels to each of these centres has a separate contract with that NHS trust. A service level agreement (SLA) is also required by each of these centres. On the whole, the travelling team is not dependent on local staff to run the clinic and can perform these independently. Laboratory testing is however required locally for the routine processing and requires funding. Phlebotomy is also occasionally provided by the

local phlebotomists where available. In the Scottish clinic, there is a local consultant haematologist who also sees patients as part of the national PNH team.

At both centres, there is a nationally commissioned liver specialist unit on site, which is consulted for patients with liver complications of PNH. We benefit greatly from the expertise within the hepato-biliary nationally commissioned service particularly in view of the radiological expertise and the clinical expertise as complications of PNH may involve thrombosis in the liver.

There is a national PNH patient group that has recently been established. There are no screening services relevant to PNH.

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

Governance:

- providers will ensure that clinical teams will have inbuilt time and resources for continuous professional development, educational and service developments
- the facilities and environment require to be safe and appropriately staffed to deliver and care for these complex cases
- incidents recorded and investigated
- annual report of morbidity and mortality
- annual report of complaints and outcomes of recommendations

This section should provide assurance that the proposed service meets national standards. This includes assurance that:

- practitioners are competent
- the environment is safe and accessible
- on-going clinical audit is in place
- arrangements for incident reporting and follow up are outlined
- practitioners will participate in continuous professional development and networking (to be built into roles within the service)

4. Key Service Outcomes

Outcomes reported:
Mean number of transfusions in a 12 month period, anonymised by patient.

There will be a continual audit cycle across the service. This will include:

- feedback from patients and their families through regular questionnaires
- continued reporting of the number of patients seen within the PNH service
- reporting of number of patients on eculizumab therapy
- reporting of any wastage within the service

- patients routinely entered into the global PNH registry in which a record of health outcomes including patient- reported outcomes are collected. This will
- enable an overview of the effectiveness of the interventions within the PNH service

Service improvement will be continually ensured through areas such as:

- the appropriate investigation and management of complaints
- monitoring information on the effectiveness of interventions such as the rate of transfusions and complications (i.e. thrombosis) for patients receiving eculizumab
- regular feedback to NHS England regarding patient outcomes
- learning good practice from other specialist services
  service user feedback/patient and public involvement through regular surveys
- continued research within the service and publication of the results of PNH-related research
- the development of appropriate policies and guidance on best practice, such as the recent development of meningococcal guidelines for patients on eculizumab by liaison with the National Reference Centre for meningococcal disease and key opinions from within the National Health Service (immunologists and microbiologists)
- modifying the service such as additional outreach clinics in new locations as needed

Service improvement may be stimulated through other areas such as:

- monitoring information
- provider feedback
- learning from other services

5. Location of Provider Premises

Outreach clinics will be held at suitable locations around the country.

These hospitals provide laboratory services, as well as consulting rooms for the clinics which are held approximately every 12 weeks. There are provider-to-provider SLAs either agreed or being developed for each of these sites.

Healthcare-at-Home are contracted to deliver eculizumab in the patient's homes. This service is funded by Alexion but managed directly by the national PNH

service.

Specialist PNH clinics are held at least weekly in Leeds Teaching Hospital NHS Trust and King's College Hospital NHS Foundation Trust, London. In addition outreach clinics are held at least every 12 weeks in Birmingham, Bristol, Oxford, Southampton, Peterborough and Monklands Hospital, Airdrie.

Eculizumab treatment is given as an intravenous infusion every two weeks in the patient's home by Healthcare-at-Home under the directions of the national PNH service.

The PNH service recognises that there may possibly be a requirement to hold outreach clinics at other locations across the country and patient demographics are reviewed regularly to determine the viability of additional clinic locations.

Appendix 1

NOTIFICATION OF ECULIZUMAB PRESCRIBING EVENT BY NATIONAL PNH CENTRE	NHS England

Centre submitting notification form:	
Leeds Teaching Hospitals ☐ **NHS Trust**	Kings College Hospital ☐ **NHS Foundation Trust**

Reason for notification form:			
Patient commencing therapy	☐	Change of demographic info	☐
Change of dose	☐	Transfer of care to alt. provider	☐
Patient discontinuing therapy	☐	Change in NHS eligibility	☐
Notification of missed dose	☐	Patient discharged from service	☐
Change of homecare status	☐	Patient deceased	☐

Patient details:

Hospital Number

Date of Birth / /

Sex Male ☐ Female ☐

Patient's GP Practice Code

Patient's Responsible PCT

Patient's Residential Postcode

Treatment eligibility criteria:

Transfusion dependent (4 or more in last 12 months) ☐

Thrombosis related to PNH ☐

Complications associated with haemolysis:

1. Renal impairment ☐
2. Pulmonary hypertension ☐

Pregnancy (and for at least 3 months post partum) ☐ Haemolytic PNH ☐ Does not meet these criteria but agreed by exceptions process ☐
Agreed exception to treatment eligibility criteria:

Reason for exception:	Exception reviewed and agreed by: Date Agreed: / /
Details of exception: *Please provide detailed rationale for exceptional circumstance and in the case of pregnancy patients expected delivery date...*	

Prescription Details:	
INITIATION REGIME Standard regime of 600mg per week for 4 Weeks? Yes ☐ No ☐ If no, please provide details: Date of First Infusion: / / Date of Last Infusion: / /	**MAINTAINANCE REGIME** Standard regime of 900mg per fortnight? Yes ☐ No ☐ If no, please provide details: Date of First Infusion: / / Date moved to Homecare: / / Date of Last Infusion: / /

Missed dose information:
A missed dose is defined as a dose that the patient does not receive either on the planned infusion date or as a catch-up dose in advance of the next planned infusion.

Date of Missed Dose / /

Was the dose prepared for administration:

Yes ☐ No ☐

What is the reason that the patient missed the dose?

Notification completed by:

Name of completing member of staff

Date / /

FOR NHS ENGLAND USE ONLY:

Date Received:	Date Processed:	Processed by:	NHS ENGLAND Patient Number:	NHS ENGLAND Script Number:

Appendix 2

National criteria for the use of eculizumab for PNH in England

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired haemolytic anaemia that is associated with intravascular haemolysis, thrombosis and an association with aplastic anaemia.[1-3] PNH is due to a clonal expansion of abnormal haematopoietic cells that are exquisitely sensitive to the uncontrolled activity of terminal complement. In its most severe form PNH leads to severe anaemia with patients frequently being transfusion dependent for many years (if not indefinitely). In addition to the anaemia, patients suffer from the direct effects of intravascular haemolysis that result in the absorption of nitric oxide, a key molecule in homeostasis, leading to smooth muscle dysfunction. This often results in severe disabling abdominal pain, severe dysphagia, profound lethargy and erectile dysfunction. Approximately half of patients suffer from thrombosis, often in major vessels, and historically a third of patients die as a direct result of thrombotic complications.[1,4] In addition the haemolysis in PNH results in renal failure in over half of patients and approximately half of patients develop pulmonary hypertension. PNH can occur at any age but usually presents in early adulthood and in most patients will persist for the remainder of the patient's life. Approximately half of patients with PNH die as a direct result of their disease, many others are transfusion-dependent for decades and for most patients with haemolytic PNH the disease has a major impact on the patient's quality of life. Pregnancy is extremely high risk in PNH with reported maternal mortalities of up to 20%, predominantly resulting from thrombotic complications, and reports of a high incidence of foetal loss.[5]

Most of the symptoms, complications and anaemia are due to the uncontrolled activity of complement on the abnormal PNH cells. Eculizumab is a monoclonal antibody that blocks the activation of terminal complement and was approved for the treatment of PNH in 2007.[6-8] Eculizumab stops the intravascular haemolysis in PNH rendering most patients transfusion independent and having a dramatic effect on the quality of life for most patients enabling them to return to normal activities and usually back to work. In addition, eculizumab stabilizes or reverses the renal failure of PNH,[9] prevents the occurrence or extension of thrombotic complications of the disease[10] and improves the pulmonary hypertension associated with the disease.[11] Recent data demonstrates that eculizumab prevents most of the complications of PNH, including during pregnancy,[12] and improves the survival to be equivalent to normal.[13]

Indications for the treatment with eculizumab in England

1. Any of the following categories of patients:
2. transfusion dependent (four or more transfusions in 12 months)
3. thrombosis related to PNH
   complications associated with haemolysis
   a) Renal failure
   b) Pulmonary hypertension

4. pregnancy (and for at least 3 months post partum)
5. haemolytic PNH with all of the following:
   a) LDH >1.5 ULN
   b) severe anaemia (Hb <9.0g/dl) or at least 2 transfusions in the last 3 months
   c) symptoms associated with haemolysis
6. exceptional cases in which eculizumab is considered appropriate (not fulfilling the above criteria) will be approved through discussion between the two nationally commissioned PNH services and NHS England