Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: *Professor Tim Goodship*

Name of your organisation: *aHUS Action*
Are you (tick all that apply):

- **a specialist in the treatment of people with the condition for which NICE is considering this technology?** Yes, I have been interested in this condition for nearly 20 years and now lead the interim national service for aHUS at the Newcastle upon Tyne Hospitals NHS Foundation Trust.

- **a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?** Yes, I was joint lead author of the recent *New England Journal of Medicine* paper describing the results of the initial studies and senior author of the 2010 UK aHUS guidelines published in the *British Journal of Haematology*.

- **an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?** I am employed by Newcastle University but hold an Honorary Consultant contract with Newcastle upon Tyne Hospitals NHS Foundation Trust.

- **other?** I am Chairman of Kidney Research UK.

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Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS)

What is HUS? HUS is a thrombotic microangiopathy whereby small blood vessels become blocked by thrombus. The small blood vessels within the glomeruli (filters) of the kidney are particularly (but not exclusively) affected. Because blood flow within these vessels is essential for the formation of a filtrate (glomerular filtration) which results in urine it is not surprising that kidney failure is a key feature of this disease. There are two forms of haemolytic uraemic syndrome. The "typical" form of HUS usually occurs after a preceding infection with an enterohemorrhagic strain of the bacteria *E.coli* (EHEC). These strains produce a toxin (shiga toxin) which causes activation and death of the endothelial cells lining the small blood vessels within glomeruli. Most patients with this form of HUS recover renal function but may need a temporary period of dialysis. In atypical HUS (aHUS) there is usually no evidence of a preceding EHEC infection and the long-term prognosis has until recently not been good. Despite treatment with plasma exchange or plasma infusions the majority of patients within two years of presentation require long term renal replacement therapy. For these individuals the outcome of transplantation has not until recently been good with a high percentage of individuals losing the transplant as a result of recurrent disease.

What is the cause of aHUS? In the past two decades there has been a substantial increase in our understanding of the underlying cause of aHUS. A series of studies have shown that inherited and/or acquire abnormalities of the complement pathway are found in ~60% of aHUS patients[1]. Complement is a part of the innate immune system and plays a pivotal role in detecting and destroying pathogens. Because it is not discriminatory there are a series of complement regulators which prevent complement mediated host cell damage. Inherited abnormalities (mutations and genomic disorders) have been reported in three complement regulators (factor H, factor I and CD46) and two complement activators (C3 and factor B) which result in excessive activation of complement at the surface of endothelial cells[1]. Acquired abnormalities in the form of autoantibodies against factor H and factor I have also been described[2, 3].

How is aHUS diagnosed? A diagnosis of aHUS should be considered whenever a patient presents with features consistent with a renal thromobotic microangiopathy, namely thrombocytopenia, microangiopathic haemolytic anaemia and acute renal failure. However, there are other conditions that can present with similar features that need excluding before a diagnosis of aHUS can be made. These include typical (EHEC) HUS, drug induced (cisplatin, gemcitabine, mitomycin, clopidogrel, quinine, interferon α,β, Anti-vascular endothelial growth factor, campath, cyclosporine, tacrolimus and ciprofloxacin), thrombotic thrombocytopenic purpura (TTP), SLE, antiphospholipid antibody syndrome, HIV, scleroderma and cobalamin C disease[4]. Appropriate tests for these should be undertaken. Because of the thrombocytopenia a renal biopsy is not always undertaken but the presence of a thrombotic microangiopathy on biopsy in the absence of the aforementioned other associated diseases confirms a diagnosis of aHUS.

What is the prevalence and incidence of aHUS in England? In the application to establish a national aHUS service that I submitted in 2012, on behalf of the Newcastle upon Tyne Hospitals NHS Foundation Trust, to the Advisory Group for National Specialised Service (AGNSS) we derived an estimate of the prevalence

and incidence of aHUS in England from a survey undertaken in 2012 of all renal units. We asked each unit to provide the following information on prevalent patients - age, gender, date of first presentation, renal status (dialysis, transplant, chronic kidney disease or normal), use of plasma therapy, use of eculizumab and where appropriate status on the transplant list. To obtain data on the incidence of aHUS within the UK we asked each unit to provide for 2009 and 2010 the following information on every patient who presented for the first time with aHUS- age, gender, outcome (normal renal function, chronic kidney disease, dialysis or deceased) and use of plasma therapy. This showed there to be a minimum of 139 prevalent patients in England (plus a further 23 in Scotland, 12 in Wales and 3 in Northern Ireland). Of the 139 patients in England 43 were under the age of 18, 90 were female and 49 male. There were a minimum of 46 patients undergoing dialysis, 9 patients undergoing regular plasma therapy, 29 patients with chronic kidney disease, 32 patients with normal renal function and 16 patients with a functioning renal transplant. 10 patients were active on the "waiting list" for a renal transplant, 9 of these were on dialysis and 1 had advanced CKD. There were 7 patients being treated at that time with eculizumab. 1 adult was in the extension phase of the eculizumab trials and 6 children were receiving the drug funded through an IFR by the respective PCT.

From this data we estimated that the prevalence of the disease in England was ~2.7 per million population. However, the prevalence for the population (2.545 million) covered by NHS North East which includes renal units in Newcastle upon Tyne (adult and paediatric), Middlesbrough, and Sunderland was significantly higher at ~5.5 per million population. Because of our longstanding interest in aHUS we opined that the ascertainment of patients with aHUS in our own centre in Newcastle and those in Sunderland and Middlesbrough is high. In other units in England we suspected that there were patients in whom it was not recognised that aHUS is the underlying cause of their renal failure. For instance we had been asked to undertake genetic screening in two patients who developed post-transplant HUS. In both the original clinical diagnosis was malignant hypertension but in retrospect their presenting features were compatible with a diagnosis of aHUS. In one we found a mutation in the gene encoding factor H. Applying the prevalence of the North East to the rest of England gave a total of 286 patients rather than 139.

In 2009 and 2010, 11 and 14 patients respectively presented with aHUS for the first time in England. Of these 25 patients 17 were under the age of 18. Assuming a population of England of 52 million this would give a minimum incidence of 0.21/million population for 2009 and 0.27 for 2010. As with the prevalent population we believed that ascertainment of all incident patients with aHUS was not complete. We at that time were , therefore, of the opinion that the true incidence of aHUS was closer to 0.40 per million population which gives 21 new patients per year of whom we estimated 11 would be children and 10 adults. Since that time our collaborators in France have published a report on patients presenting with aHUS in France in the period 2000 – 2008 [5] . During that time 214 patients were diagnosed with aHUS giving an incidence of 0.23 per million population.

On the 1st April 2013 NHS England implemented an interim policy for funding the treatment of aHUS with eculizumab. This included all incident patients. All requests for such funding have to come through Newcastle and accurate figures are therefore now becoming available on the number of patients who might in the future need eculizumab. Since the 1st April 2013 there have been 9 new patients (7 adult and 2

paediatric) treated with eculizumab under this interim policy. From this we predict that there will ~22 incident patients per year giving an incidence of 0.42 per million population. This is very close to our original estimate of 0.40 per million population.

How is the condition currently treated in the NHS? Until recently the only treatment available for aHUS patients within the NHS has been either plasma exchange or plasma infusion (collectively known as plasma therapy). A minority of patients respond to this treatment and in those that do it is often necessary to continue with long-term prophylactic treatment to prevent relapses. The majority of patients do not respond and within two years of presentation need long term dialysis. Recognising that excessive complement activation was the underlying mechanism in the pathogenesis of aHUS led to trials of the complement inhibitor eculizumab in the disease. The successful outcome of these trials led in 2011 to both the FDA and EMA approving the use of eculizumab in aHUS. Subsequently an application was submitted to the Advisory Group for National Specialised Services (AGNSS) for a national service for aHUS in England including use of eculizumab. This was considered by AGNSS in June 2012. Despite a positive recommendation to Ministers it was decided that the affordability of eculizumab should be considered by NICE, hence the current Highly Specialised Technology Evaluation. However, on the 1st April 2013 NHS England implemented an interim policy for the use of eculizumab in aHUS whereby funding was made available for all newly diagnosed aHUS patients. This policy was subsequently extended to all aHUS patients to prevent the development of irreversible renal failure. The Clinical Priorities Advisory Group of NHS England considered this policy at a meeting in August and recommended that funding should be made available for all aHUS patients on dialysis to receive eculizumab to enable a successful renal transplant to be undertaken. Ratification of this decision by NHS England's Directly Commissioned Services Committee is awaited.

Is there significant geographical variation in current practice? Within England the only access to eculizumab within the NHS prior to the NHS England interim policy was through an IFR submitted to the appropriate PCT. Whilst some IFR applications were successful there was significant geographical variation. It was apparent that an IFR application for the same clinical situation could meet with a different outcome depending on the PCT. In Scotland, Northern Ireland and Wales the only access to eculizumab is still through an IFR/IPTR with the same geographical disparity.

Are there differences of opinion between professionals as to what current practice should be? The current interim policy implemented by NHS England enables clinicians to apply for funding for eculizumab for patients under their care through the interim national aHUS service in Newcastle. To do this clinicians are requested to complete an "aHUS checklist" (attached as an appendix to this document). This is then reviewed by the four clinicians in Newcastle responsible for the interim national aHUS service (Tim Goodship, Neil Sheerin, David Kavanagh and Sally Johnson). Provided that a consensus is reached that the diagnosis is aHUS and that eculizumab would be beneficial then NHS England are approached for funding. It is, therefore, the local clinician who initially decides that eculizumab would potentially be beneficial. Most clinicians consider that eculizumab will be first line therapy for aHUS in the future but we are aware of a few who would consider

eculizumab only after there has been a failure to respond to plasma therapy. Whether all patients need to continue long term therapy with eculizumab is a more contentious issue. We are of the opinion that this would best be examined in the setting of a randomised controlled trial.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? Plasma therapy (either plasma exchange and/or plasma infusions) is the only current alternative to eculizumab. There have been no trials examining the use of plasma exchange in aHUS and its use predates our current understanding of the molecular mechanisms underlying the disease. Despite treatment with plasma therapy 65% of patients within one year of presentation will have died or have irreversible renal failure [6]. A few patients do respond to plasma therapy but in many it is necessary to continue long term prophylactic treatment to prevent relapses. There are significant disadvantages associated with plasma therapy. Major complications (such as death, cardiac events and infection) occur in 25% of patients[7]. Plasma exchange in children has a particularly high rate of complications [8]. The change in quality of life in patients who had previously been treated with plasma therapy and were treated with eculizumab as part of the prospective trials in aHUS was profound [9]. Plasma therapy is, however, the treatment of choice in patients with TTP. We, therefore, recommend that plasma therapy be commenced in all patients with a renal thrombotic microangiopathy until a diagnosis of TTP is excluded by measurement of ADAMTS13 activity.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Several studies have shown that patients with mutations in the gene encoding membrane cofactor protein (*CD46*) have a less severe phenotype than other groups of patients [5, 10]. Both the risk of developing end-stage renal failure at first presentation and the risk of recurrent disease post-transplant are significantly lower in this group. At first presentation it is not going to be possible to know the results of mutation screening before eculizumab is commenced. If a patient is subsequently found to have only a mutation in *CD46* then it is probable that the eculizumab can be withdrawn. If, however, a patient with a *CD46* mutation has multiple recurrences then eculizumab would prevent further episodes. In an aHUS patient on dialysis who is known to have only a *CD46* mutation there is no need to consider prophylactic eculizumab [11]. Likewise the phenotype of patients with factor H autoantibodies alone has been found to be less severe [3, 12]. Again it is possible that eculizumab could be withdrawn in such patients when they present for the first time and not be used prophylactically in such patients undergoing transplantation.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? The prospective trials of eculizumab showed that patients without a known mutation or factor H autoantibody responded as well to eculizumab as those with a known mutation [9]. However, two recent studies have shown either homozygous or compound heterozygous mutations in the gene encoding diaclyglycerol kinase epsilon [13-15]. This is an enzyme that regulates levels of protein kinase C. This is not part of the complement pathway and aHUS patients with mutations in this gene would not be expected to respond to eculizumab. It is

probable that there are other non complement genes that explain the disease in the ~35% of patients who have not been found to have a complement abnormality.

What is the likely impact of the technology on the delivery of the specialised service? When an application was originally submitted to AGNSS it was for the establishment of a national aHUS service including eculizumab. NHS England's interim policy is currently administered through an interim national aHUS service in Newcastle. This is not currently funded and is provided by the Newcastle upon Tyne Hospitals NHS Foundation Trust on a "goodwill" basis. The service consists of three adult nephrologists (Tim Goodship, Neil Sheerin and David Kavanagh) and one paediatric nephrologist (Sally Johnson). All have considerable experience in complement mediated renal disease. The service provides a means by which clinicians throughout England can seven days a week obtain access to eculizumab for aHUS patients. The Newcastle upon Tyne Hospitals NHS Foundation Trust also provides a national (UK Genetics Testing Network approved) service for genetic screening of aHUS patients (copy of request form attached). The service has developed guidelines for the use of eculizumab to prevent the recurrence of aHUS post renal transplant (attached). Thus all the components necessary to deliver eculizumab within a national specialised service are already in place and functioning.

Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)? In order to run a national aHUS service on a permanent basis additional staff will be needed. In the original application to AGNSS the Newcastle upon Tyne Hospitals NHS Foundation Trust requested additional consultant staff, clinical nurse specialists, a manager, secretarial support, IT support and laboratory support.

We envisaged that the service would a shared-care service delivered by a centre at the Newcastle upon Tyne Hospitals NHS Foundation Trust with responsibility for both paediatric and adult patients. The national aHUS service would be responsible in partnership with each patient's local clinician for developing an individualised care plan. The service would review the history and investigations already undertaken on each patient. Where necessary the service would organise additional special investigations necessary to confirm the diagnosis of aHUS. The service would approve the local prescription of eculizumab with delivery of the therapy initially in hospital and later at home using a home care provider. The service would be responsible in partnership with the local clinician for the ongoing management of all patients receiving eculizumab including the appropriate prevention of meningococcal infection.

The service would be primarily telemedicine based. Patients and their family/carers would be given the option of either a face to face consultation in Newcastle or a teleconsult. The Newcastle upon Tyne Hospitals NHS Foundation Trust has implemented secure software (Polycom CMA) for videoconsults. This has already been used successfully in the interim service. These virtual consultations would ensure that the travelling time for the patients, their families and all clinical staff (local and those of the aHUS service) is kept to a minimum.

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If the technology is already available, is there variation in how it is being used in the NHS? Eculizumab has been used to treat paroxysmal nocturnal haemaglobinuria (PNH) within the NHS since 2007. In 2009 a national service for PNH was established based in two centres, St James's Hospital in Leeds and King's College Hospital in London. Within this service eculizumab is prescribed centrally and patients are seen in outreach clinics.

Is it always used within its licensed indications?
If not, under what circumstances does this occur? No. Eculizumab has been used to treat membranoproliferative glomerulonephritis [16, 17], antiphospholipid antibody syndrome [18], refractory thrombotic thrombocytopenic purpura[19], antibody-mediated transplant rejection[20], EHEC associated HUS[21] and myasthenia gravis[22]. For these conditions the reports are anecdotal and there is no trial data available yet.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendation. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom were published in the *British Journal of Haematology* in 2010 (attached)[23]. The GRADE system (http://www.gradeworkinggroup.org) was used to classify the strength of recommendations (strong or weak) and the quality of evidence (high, moderate, low and very low) [24]. The guidelines were produced on behalf of the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. The final section of the guidelines on "Clinical Trials in aHUS in the UK" mentions that "Clinical trials of complement inhibitors in patients with aHUS have recently commenced in the UK. The first agent to be assessed is eculizumab. Anecdotal case reports have suggested a potential role for this agent in the management of aHUS" and that "The outcome of trials with agents such as eculizumab is eagerly awaited and will undoubtedly inform future versions of these guidelines." Work to produce a revised version of these guidelines will soon commence.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
Currently patients who present for the first time with aHUS are treated with either plasma therapy with either plasma exchange and/or plasma infusions. Plasma exchange requires central venous access to be placed with all the associated risks of this such as bleeding, development of a pneumothorax/haemothorax and catheter related infection. The treatment is then usually undertaken daily.with, typically in adults, 3L of the patient plasma being removed and replaced with 3L of replacement fluid. The replacement fluid is usually plasma which can be either fresh frozen plasma or a detergent treated preparation such as Octoplas. Rarely albumin alone is

used. There are significant risks associated with the use of plasma products including allergic reactions and electrolyte imbalance. In most aHUS patients plasma exchange is undertaken daily until either there is evidence of a response (improvement in platelet count, LDH level, haptoglobins and renal function) or it becomes obvious that renal function is not going to recover. Further evidence for the latter can be obtained by undertaking a renal biopsy. In some patients there is evidence of an improvement in the markers that define a thrombotic microangiopathy – platelet count, LDH, haptoglobins and haemoglobin – without any improvement in renal function suggesting that irreversible renal damage has been sustained. Plasma therapy is, therefore, a treatment which has never been shown in a clinical trial to be effective in the treatment of aHUS but is associated with significant mortality and morbidity. In contrast eculizumab has been shown in prospective clinical trials to be an effective form of therapy with only one major side-effect (meningococcal disease) the risk of which is small. Eculizumab is given as a peripheral intravenous infusion over ~45 mins. It is initially given weekly for 5 weeks and then on alternate weeks. The infusions are tolerated well and can, once the patient is in the convalescent stage, be given at home. The major risk associated with the use of eculizumab is meningococcal disease. Because of this all patients are vaccinated with a tetravalent preparation. This does not currently provide cover against group B strains but a group B specific vaccine is undergoing trials at present. Because of this we recommend that all aHUS patients in the UK receive long term prophylactic antibiotics with either penicillin or if allergic erythromycin. We also emphasise to patients on eculizumab that they must seek early medical attention if they develop a severe or prolonged “flu-like”illness. Eculizumab has been used to treated PNH since 2008. This experience has shown that the incidence of meningococcal disease in individuals receiving eculizumab is 0.5 events per 100 years treatment. Worldwide there have been 2 deaths from meningococcal disease associated with delay in diagnosis and treatment. Ecuzliumab is therefore well tolerated and associated with few side effects. In the prospective trials there was a pronounced improvement in quality of life which was highly significant.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. The interim national service for aHUS in Newcastle requests clinicians who wish to use eculizumab to complete and return a diagnostic check list (attached). This is then considered by the four physicians associated with the service (Tim Goodship, Sally Johnson, Neil Sheerin and David Kavanagh). Once a consensus as to whether the patient has aHUS and whether they would benefit from treatment with eculizumab is achieved then a direct application for funding is made to NHS England. Approval is obtained within 24 hours and treatment started. This system has worked well without any significant delay in the onset of therapy. The complement tests (genetics and autoantibodies) are sent by the local clinician to Newcastle. The results of these are available within ~8 weeks. We meet every 4 weeks to formally review the progress of all aHUS patients being treated with eculizumab. We will currently consider withdrawing eculizumab in the following circumstances.

a. A newly diagnosed patient who does not have any complement abnormality (genetic or autoantibody) who despite at least four months of treatment does not show any recovery of renal function and remains on dialysis. In these patients we

recommend measurement of platelet count, LDH, haptoglobins and haemoglobin every two weeks. We use these indices to determine whether there is any recurrence of an extra-renal TMA which might need reintroduction of eculizumab.

b. A newly diagnosed patient who on screening is found to have only a mutation in MCP (CD46) and has completely recovered renal function with no evidence of an ongoing TMA. Studies undertaken before the use of eculizumab has shown that the natural history of the disease in such patients is often good with spontaneous complete recovery of renal function. If patients developed frequent relapses then use of long-term prophylactic eculizumab would be appropriate.

c. A newly diagnosed patient who on screening is found to have only factor H autoantibodies. The prognosis in this group of patients is good with many patients not relapsing.

We would not consider withdrawing eculizumab in the following circumstances

a. In a patient who had received eculizumab to prevent recurrent disease post transplant where there was a history of a previous transplant being lost to recurrent disease.

b. In a patient known to have a mutation which is associated with a high rate of recurrence and a poor prognosis (for instance the *CFH/CFHR1* hybrid).

In all other patients we would only consider withdrawing eculizumab in the context of a randomised clinical trial.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? We are very familiar with the evidence base for eculizumab. Two of us (Tim Goodship and Neil Sheerin) were authors on the *New England Journal of Medicine* paper and Tim Goodship was joint senior author. The trials were conducted in two groups of aHUS patients, those who were undergoing long term plasma therapy to maintain remission and those who were resistant to treatment with plasma therapy. The latter group included newly diagnosed patients, patients experiencing a relapse in their native kidneys and patients experiencing a recurrence post-transplant. So in both these studies there was a requirement for the patients to be undergoing plasma therapy Two further prospective trials have been undertaken one in adults and one in children. The results of these have yet to be reported but in both there was no requirement for the patients to be undergoing plasma therapy. In England we are currently aware of only one patient who is undergoing prophylactic regular plasma exchange to prevent relapses. Within the current interim national service we recommend that patients receive plasma therapy until a diagnosis of TTP is excluded on the basis of ADAMTS13 activity. The national service for TTP run by Dr Marie Scully at University College Hospital provides a rapid turn-around for this assay such that eculizumab can be commenced within 48 hours of presentation if the

ADAMTS13 assay excludes TTP. Within the national service we support the right of the local clinician to treat an aHUS patient with plasma therapy if they are of the opinion that it is the most appropriate therapy. Once eculizumab is commenced within the national service the patient care is shared between the national centre and the local clinician. Our experience since the 1st April is that local clinicians are both keen and happy to undertake the majority of the care.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Both within the clinical trials and in those patients treated with either compassionate supply from Alexion or funded through the PCT, Trust or NHS England we have seen very few side effects that affect either the management of the condition or the quality of life of the patient. There has been one case of meningococcal meningitis in a trial patient. This patient although vaccinated was not receiving prophylactic antibiotics at that time. This infection was diagnosed early and rapidly responded to treatment. Subsequently the patient was keen to stay on eculizumab but is now like all other patients in the UK receiving prophylactic antibiotics. The only side effect that was not apparent in the clinical trials has been an exacerbation of severe migraine in the 24 hours post administration of eculizumab in one patient. This has been reported to Alexion and also through the "yellow card" system.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined. A national registry of aHUS patients in the UK is in the process of being established as part of an integrated strategy developed by the Renal Association and the British Association for Paediatric Nephrology for patients with rare renal diseases (www.rarerenal.org). Currently only a few patients with aHUS have been entered into the Rare Renal Disease Registry (www.renalradar.org) and as such there is not sufficient detail to contribute to this evaluation. There is also an international registry of aHUS patients sponsored by Alexion which has just been established. Less than ten patients from England have been entered into this registry to date.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

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If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The interim policy for funding of eculizumab for aHUS implemented by NHS England on the 1st April has recently been expanded to include virtually all patients in England who would benefit from treatment. An interim national service has been established in Newcastle to run this service. If NICE recommend funding for eculizumab for aHUS then the fundamental framework necessary to deliver a long term service will already be in place.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

We do not believe that any of these conditions would apply to this evaluation.

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Bibliography

1. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med.* Oct 22 2009;361(17):1676-1687.

2. Kavanagh D, Pappworth IY, Anderson H, et al. Factor I autoantibodies in patients with atypical hemolytic uremic syndrome: disease-associated or an epiphenomenon? *Clin J Am Soc Nephrol.* Mar 2012;7(3):417-426.

3. Moore I, Strain L, Pappworth I, et al. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4 and with mutations in CFH, CFI, CD46, and C3 in patients with atypical haemolytic uraemic syndrome. *Blood.* Oct 27 2010;115(2):379-387.

4. Kavanagh D, Goodship T. Haemolytic uraemic syndrome. *Nephron Clinical Practice.* 2011;118(1):c37-42.

5. Fremeaux-Bacchi V, Fakhouri F, Garnier A, et al. Genetics and Outcome of Atypical Hemolytic Uremic Syndrome: A Nationwide French Series Comparing Children and Adults. *Clin J Am Soc Nephrol.* Jan 10 2013.

6. Caprioli J, Noris M, Brioschi S, et al. Genetics of HUS: the impact of MCP, CFH and IF mutations on clinical presentation, response to treatment, and outcome. *Blood.* Apr 18 2006;108:1267-1279.

7. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood.* Nov 18 2010;116(20):4060-4069.

8. Michon B, Moghrabi A, Winikoff R, et al. Complications of apheresis in children. *Transfusion.* Oct 2007;47(10):1837-1842.

9. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med.* Jun 6 2013;368(23):2169-2181.

10. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol.* Oct 2010;5(10):1844-1859.

11. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Fremeaux-Bacchi V. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nature Reviews Nephrology.* Nov 2012;8(11):643-657.

12. Dragon-Durey MA, Sethi SK, Bagga A, et al. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. *J Am Soc Nephrol.* Dec 2010;21(12):2180-2187.

13. Lemaire M, Fremeaux-Bacchi V, Schaefer F, et al. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. *Nat Genet.* May 2013;45(5):531-536.

14. Ozaltin F, Li B, Rauhauser A, et al. DGKE variants cause a glomerular microangiopathy that mimics membranoproliferative GN. *J Am Soc Nephrol.* Feb 2013;24(3):377-384.

15. Quaggin SE. DGKE and atypical HUS. *Nat Genet.* May 2013;45(5):475-476.

16. McCaughan JA, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. *Am J Transplant.* Apr 2012;12(4):1046-1051.

17. Bomback AS, Smith RJ, Barile GR, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. *Clin J Am Soc Nephrol.* May 2012;7(5):748-756.

18. Shapira I, Andrade D, Allen SL, Salmon JE. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis And Rheumatism.* Aug 2012;64(8):2719-2723.

19. Chapin J, Weksler B, Magro C, Laurence J. Eculizumab in the treatment of refractory idiopathic thrombotic thrombocytopenic purpura. *Br J Haematol.* Jun 2012;157(6):772-774.

20. Stegall MD, Diwan T, Raghavaiah S, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant.* Nov 2011;11(11):2405-2413.

21. Wong EK, Goodship TH, Kavanagh D. Complement therapy in atypical haemolytic uraemic syndrome (aHUS). *Mol Immunol.* Jun 27 2013.

22. Querol L, Illa I. Myasthenia gravis and the neuromuscular junction. *Curr Opin Neurol Neurosurg.* Aug 13 2013.

23. Taylor CM, Machin S, Wigmore SJ, Goodship TH. Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom. *Br J Haematol.* Jan 2010;148(1):37-47.

24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J (Clin Res Ed).* Apr 26 2008;336(7650):924-926.