NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust

The National aHUS Service

Annual Report 2016/17

Newcastle University

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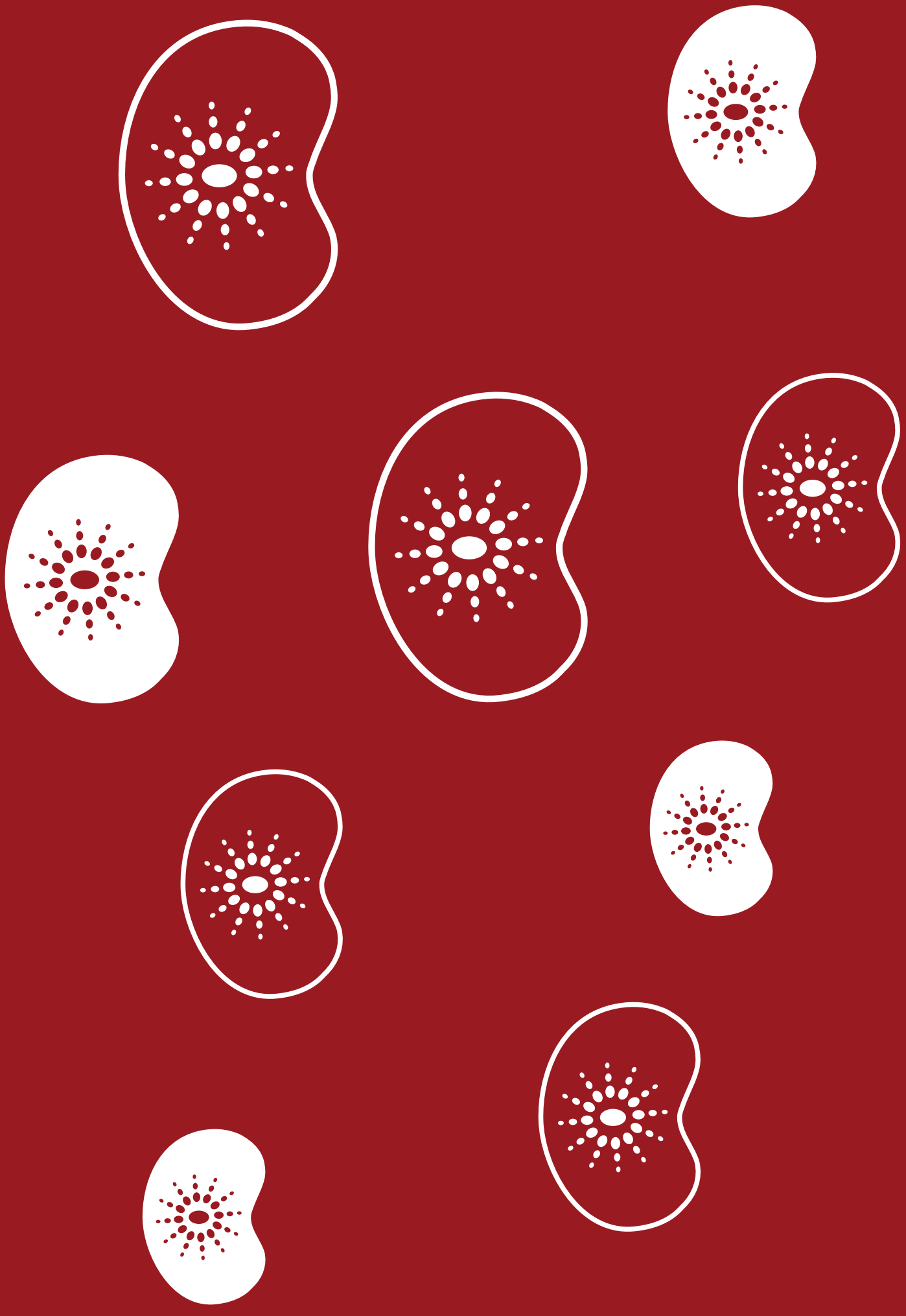


The National aHUS Service

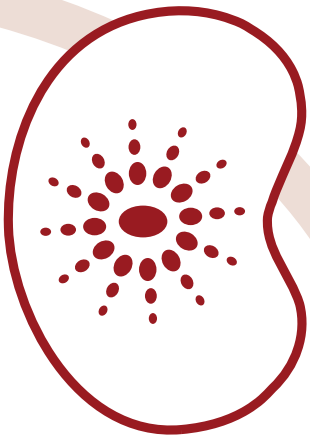
Annual Report 2016/17

aHUS
ATYPICAL HEMOLYTIC-UREMIC SYNDROME

NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

C3G
C3 Glomerulopathy

Contents



1. Overview of Performance

1.1 The National Service

The National atypical Haemolytic Uraemic Syndrome (aHUS) service was commissioned in May 2016 by NHS England (NHSE) to co-ordinate the management of patients with aHUS and other thrombotic microangiopathies. Investigation and treatment of C3 Glomerulopathy (C3G) recurring after transplantation was added to our portfolio in February 2017. The aim of our service is to provide a combined clinical, diagnostic and treatment centre for these complement mediated diseases. Our service delivers this fully integrated care pathway to expedite optimal management of patients with aHUS on a shared-care basis with the referring clinicians.

The National aHUS Service is based at the Royal Victoria Infirmary (RVI) which is part of the Newcastle upon Tyne Hospitals NHS Foundation Trust.

This report refers to the activity of the National aHUS Service which is an integral part of the National Renal Complement Therapeutics Centre (NRCTC) *(Figure 1)*. Our core team is comprised of four consultant nephrologists (3 adult and 1 paediatric), two nurse specialists and the administration team. To provide cutting edge diagnostics we also have six dedicated clinical scientists working across genetics, haematology and immunology. We are supported from an organisational point of view by the renal services directorate team based at the Freeman Hospital. The NRCTC also works closely with the Newcastle University Complement Therapeutics Research group who were responsible for the discovery of the role of complement in aHUS, which ultimately led to the successful treatment of our patients with Eculizumab.

Figure 1

1.2 Our Vision and Values

Our vision is to be a centre of clinical excellence for patients with complement mediated renal diseases, including aHUS and C3G and at the forefront of international research. Our primary core value aligns with that of Newcastle upon Tyne Hospitals NHS Foundation Trust, "putting patients at the heart of everything we do." We wish to empower our patients to be knowledgeable about the care they require and receive. Our aspiration is to encourage our patients to influence the care we deliver, enabling personalised management.

1.3 Context

Atypical HUS is a rare disease with an incidence in the UK of 0.4-0.5 per million population. It presents acutely with acute kidney injury and, not infrequently, multi-organ involvement. Without treatment the prognosis for patients was poor with 50% of patients developing renal failure or dying in the first year after presentation.

The diagnosis of aHUS is based on clinical and laboratory findings and the exclusion of other pathologies; in particular infection related Shiga Toxin (STEC)-HUS and Thrombotic Thrombocytopenic Purpura (TTP). Diagnosis can be challenging as there is no simple diagnostic test for aHUS and as a consequence treatment may be delayed which adversely affects outcome of patients.

The National aHUS Service is available 7 days a week 24 hours a day to provide diagnostic advice from clinicians experienced in the management of this disease. We also provide rapid diagnostic testing and support for clinicians to exclude other forms of Thrombotic Microangiopathy (TMA).

Eculizumab was licensed for the treatment of aHUS in 2011 having been shown to be effective in non-randomised, single arm open label studies. After initial review, preliminary interim funding for the use of Eculizumab to treat patients with aHUS in England was approved in 2013 whilst the National Institute for Health and Care Excellence (NICE) undertook further review. NICE published its guidance in 2015 recommending that Eculizumab was commissioned for the treatment of aHUS. However, reflecting the high cost of Eculizumab, NICE recommended that treatment of patients was co-ordinated through an expert centre.

For the purposes of this report the figures we are quoting are from the establishment of the National Service to the end of the financial year 2016/17 (01/06/2017 to 31/03/2017). A breakdown of the patients who were referred to the service and their outcome during this reporting period is summarised later in the report.

1.4 Service Implementation

The National aHUS Service was commissioned in June 2016. During this current reporting period the following developments have occurred:

- Appointment of two Clinical Nurse Specialists.
- Appointment of a Service manager and administrative team.
- Appointment of Adult (start May 2017) and Paediatric Nephrologist (start January 2018).
- Establishment of protocols for the investigation and management of patients with suspected aHUS and recurrent C3G.
- Implementation of shared care protocols.
- Development of information for patients and carers.
- Support for the development of a patient network.
- Establishment of the National Renal Complement Therapeutics Centre (NRCTC) to co-ordinate clinical and research programmes to offer an internationally recognised translational research group.
- Launch of the National aHUS Service website, providing information for clinicians and patients.

1.5 Our Strategy

Our six service strategic objectives reflect how we wish to meet our vision, focusing on where we are now and what we want to achieve in the future.

Providing exceptional shared care today

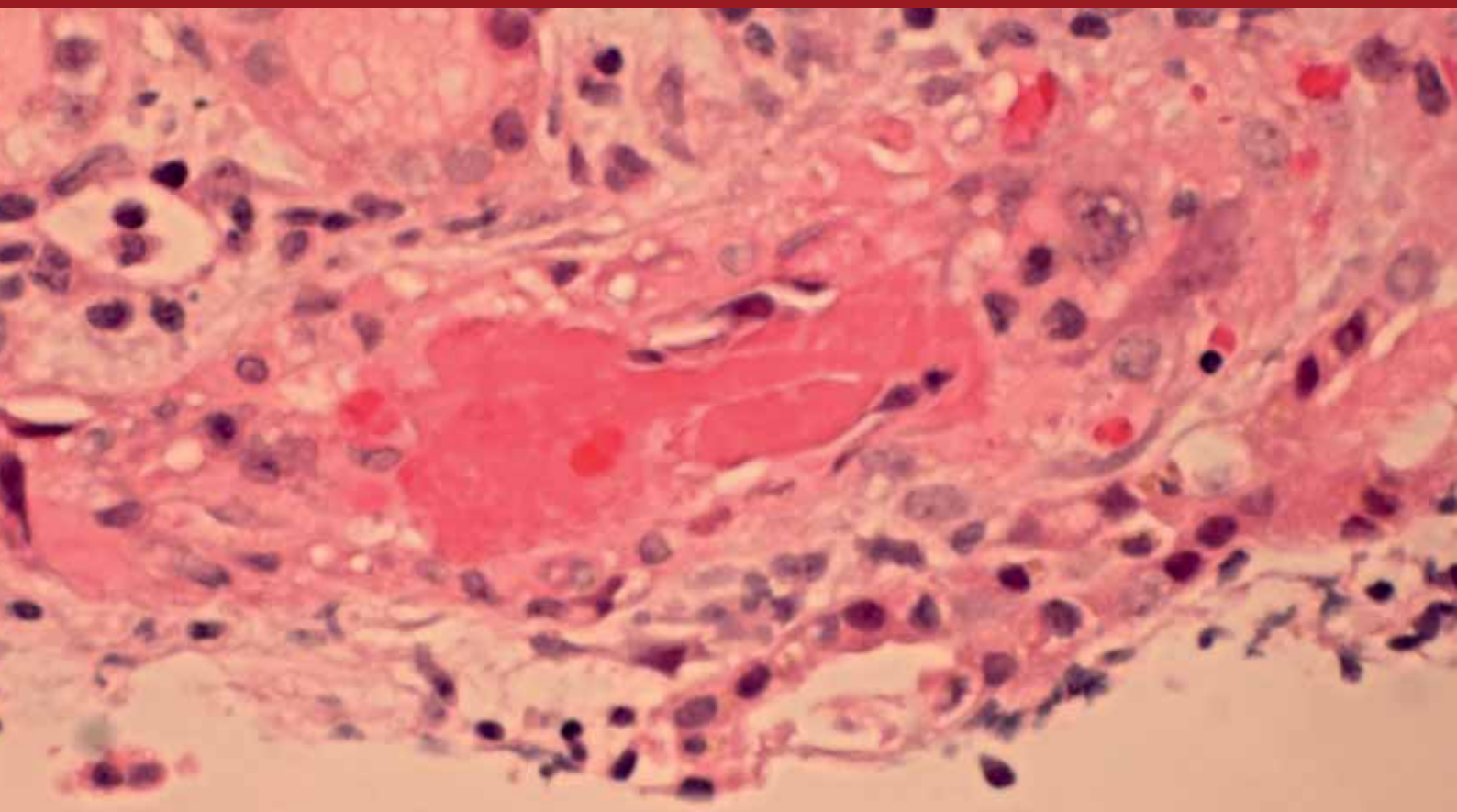
- Advice/care will be offered in a timely manner to every person contacting the National aHUS Service.
- Every person requiring advice/care from the National aHUS Service will be provided with safe and high quality advice/care. Patients and their families engaging with the National aHUS Service will receive an excellent patient experience.

Striving to improve our service

- Each member of the National aHUS Service team will be exploring ways to improve the delivery of care and advice we offer to clinicians, patients and their families.
- Each member of the National aHUS Service team will be an advocate for patients and their families.

Advancing care for tomorrow

- We will enhance the reputation of the Newcastle upon Tyne Hospitals as the provider of a Highly Specialised Service, for the UK and the world.
- We will continue to be the world leaders in complement research with our partners Newcastle University and Newcastle upon Tyne Hospitals.



1.6 Working in Partnership and Offering Seamless Care

In order for patients with aHUS to receive excellent care, it is essential that the local clinical team and National aHUS Service each understand their roles and responsibilities in delivering that care. This was highlighted in the service specification: namely to facilitate optimal patient management on a shared-care basis with referring clinicians. Therefore one of our priorities for the first year was to develop a shared care protocol. The shared care protocol was generated following an extensive consultation process with our stakeholders (clinicians/commissioners) and was approved for use by NHSE in February 2017. This protocol was initially rolled out to all incident patients with subsequent enrolment of the prevalent patients already receiving Eculizumab.

1.7 Ensuring High Quality Care that Delivers Optimal Use of Eculizumab

Combined aHUS Lab Diagnostics

In the first year of the NRCTC we have put in place a combined haematological, immunological and genetic diagnostic tool kit which allows the rapid diagnosis of atypical HUS and the secondary causes of TMA. These allow tailored management of thrombotic microangiopathies and C3 glomerulopathies.

Genetics

The Northern Genetics Service has long provided complement testing for atypical HUS and C3G. This encompassed standard sequencing of the complement genes factor H, factor I, *CD46*, *C3* and factor B in addition to determining copy number variations of several of these genes.

The Newcastle University Complement Therapeutics Research Group under Professor Kavanagh and the Northern Genetics Service under Dr David Bourne are now fully integrated to provide rapid translational benefits to patients. The aim of the combined unit is to personalise management of our patients through next generation sequencing technology either locally or via the 100,000 Genomes Project.

In the last year we reported on the presence of a *C5* genetic variant in a European population that predicts Eculizumab non-response. This testing is now routinely undertaken in our clinical lab and is immediately performed to identify patients who will not respond to Eculizumab allowing plasma exchange to be rapidly resumed. (Goodship *et al*., Blood Advances 2017).

We have also identified other non-complement genetic causes of thrombotic microangiopathies which do not respond to Eculizumab (Challis *et al*, JASN 2017). We now routinely sequence the genes *DGKε* and *MMACHC* and undertake bespoke analysis for *INF2*. This avoids ineffective treatment with Eculizumab and potentially allows other effective treatments to be instituted (e.g hydroxycobalamin in patients with *MMACHC* associated TMA).

Additionally using whole exome sequencing we have identified other diseases which may mimic HUS (e.g. Glucose-6-Phosphate Dehydrogenase ((G6PD) deficiency) (Walsh *et al* American Journal Kidney Disease 2017) and we have introduced a bespoke service where any immediate diagnosis may not be apparent.

Measurement of ADAMTS13 Activity

A key differential diagnosis for aHUS is TTP. The treatment for this condition is plasma exchange. Eculizumab does not treat TTP and therefore urgent exclusion of TTP is essential prior to commencing Eculizumab therapy. TTP can be excluded by assessing the plasma activity of a protein called ADAMTS13. Not all local centres have been able to obtain urgent ADAMTS13 results, which might previously have delayed commencement of Eculizumab. We have now developed the infrastructure for a 7 days/week, same day service for ADAMTS13 measurements where this cannot be done locally, including urgent transport of specimens to the Newcastle laboratory.

Complement Analysis

The formation of the NRCTC necessitated a broader range of complement assays to identify aHUS & C3G and to monitor treatment. Close collaboration between the Newcastle upon Tyne Hospitals Immunology Department and the University complement therapeutics research groups as part of the NRCTC has allowed the development of functional complement testing. This has already translated into new assays for disease-causing autoantibodies and assays to test for complement activation and inhibition. These tests are now offered to patients in England as part of the diagnostic panel and to monitor the efficacy of Eculizumab treatment. Separate forms for adult and paediatric patients are available.

Microbiology Specialist Laboratories

STEC-HUS is the commonest differential diagnosis of aHUS and as such rapid diagnosis is essential for timely appropriate treatment. The Public Health England (PHE) reference laboratory in Colindale provides these specialised services and we have established close links to expedite the patient results to facilitate decision making. Eculizumab predisposes to meningococcal infections and vaccination against these is mandatory for all patients receiving Eculizumab. The PHE meningococcal reference unit in Manchester is the national centre for England and we work closely with them to assess the response to vaccination to provide optimal protection against infection.

1.8 Global Reach for Optimal Patient Care

Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines

The KDIGO group is a global initiative with a primary aim of improving the treatment of kidney disease. This is achieved by the development of guidelines or publication of expert opinion on all aspects of renal disease. KDIGO recently held a meeting to generate guidance on the classification, investigation and treatment of complement mediated renal diseases. The National aHUS Service was represented at this meeting by Professor Goodship, Professor Kavanagh, Professor Sheerin and Dr Sally Johnson, recognising the expertise available within the National aHUS Service.

European Reference Network on Rare Kidney Disease (ERKNet)

ERKNet is the European Reference Network for rare kidney diseases. It is a consortium of 38 expert paediatric and adult nephrology centres across the European Union providing healthcare to more than 40,000 patients with rare disorders of the kidney. The NRCTC is proud to have been selected as a reference centre for TMA for ERKNet. ERKNet offers virtual consultation services to physicians throughout Europe who need advice for challenging cases with a rare kidney disease. The NRCTC has already demonstrated its global reach with consultations not only across Europe but also Asia, Africa and North and South America.

1.9 Education and Audit

Improving Clinician Knowledge

The team at the NRCTC is committed to improving clinician knowledge to enhance patient care. As part of this programme, we have delivered presentations to thousands of delegates across local, national and international platforms.

Ongoing Audit and Review of Practice

The NRCTC undertakes constant audit and research to optimise practice. In the last year we have reviewed all cases of autoimmune aHUS in the UK. This research, published by Brocklebank *et al* (Kidney International 2017), confirmed that in Factor H autoantibody associated aHUS treatment with Eculizumab was superior to plasma based therapies.

With our European colleagues we have reviewed the rationale for the use of Eculizumab in pregnancy in aHUS. We demonstrated that pregnancy induced HUS had a high rate of complement mutations confirming the rationale for the use of Eculizumab in pregnancy (Bruel *et al* CJASN 2017).

Nurse Education

Our specialist nurses have presented at a number of nursing study days across the country to raise the awareness of the National aHUS Service, the disease process and its treatment options. The service held its first national nursing study days in June funded from an educational grant from Alexion.

Our specialist nurses have also been successful in obtaining a place on the post graduate certificate in Genomic Medicine commencing in September 2017. The course includes a module regarding genetic counselling.

Professor Neil Sheerin is the Chief investigator for:

Stopping Eculizumab Treatment Safely in aHUS Study (SETS aHUS):

The NICE appraisal recommended the use of Eculizumab on condition that a research programme with robust methods to evaluate when withdrawing treatment or reducing the dose might occur was developed. In addition, although the product licence is for life-long Eculizumab there is growing evidence that this may not be necessary and a proportion of patients may be able to withdraw safely from treatment. A National Institute for Health Research (NIHR) Health Technology Assessment award is funding a single arm, Bayesian study of Eculizumab withdrawal in 30 patients currently on treatment. The primary endpoint is patient outcome over a two year period; and not relapse which we accept will occur but predict that relapse can be effectively treated with reintroduction of Eculizumab. The protocol will test the effectiveness of self-monitoring to detect relapse. There are also embedded health economic and qualitative arms of the study.

The protocol will be submitted for ethical and MHRA approval at the end of 2017 with a planned start date for the study in March 2018.

Professor David Kavanagh is the Chief investigator in the UK for:

ALXN1210 Trial (NCT02949128):

The ALXN1210-311 trial is a Phase 3, open-label, randomized, active-control, multicentre study to evaluate the safety and efficacy of a long acting Eculizumab analogue (ALXN1210) in adult and adolescent patients. If successful this agent would minimise drug administration to only 6 times per year.

Dr. Sally Johnson is the Chief Investigator for three multicentre studies.

ECUlizumab in Shiga-Toxin producing Escherichia Coli Haemolytic Uraemic Syndrome (ECUSTEC):

ECUSTEC is a Randomised, Double-Blind, Placebo-Controlled Trial which aims to determine whether Eculizumab reduces the severity of STEC-HUS in children. The trial is due to open in July 2017 and will recruit 134 children with STEC-HUS over the next 4 years. Twelve paediatric renal units across the UK are participating in the trial. If effective, eculizumab may reduce the number of children requiring dialysis or developing severe multi-system complications from STEC-HUS. (Funded by NIHR EME £1.8 million).

ALXN1210-312 trial:

The ALXN1210-312 trial is a Phase 3, open-label, randomized, active-control, multicentre study to evaluate the safety and efficacy of a long acting Eculizumab analogue (ALXN1210) in adolescent and paediatric patients.

National Study of MPGN and C3G:

The National Study of MPGN and C3G is a longitudinal cohort study which brings together clinical, pathological, genetic and functional data of patients with these rare but devastating complement-mediated renal conditions. The aims of the study are to understand genotype/phenotype correlation, identify novel pathogenic mechanisms and identify factors associated with disease severity. In addition we have begun to stratify patients in preparation for potential trial of therapeutic complement inhibition. Nearly 300 adult and paediatric patients across 31 centres over 5 years have been recruited. Funding has been provided by Kids Kidney Research and the NIHR Rare Disease Translational Research Collaboration.

Translational Research at the Newcastle University Complement Therapeutics Research Group

Dr Marchbank, Professor Harris and Professor Kavanagh also oversee an active bench to bedside research programme within the NRCTC. This thriving collaboration enables in-depth mechanistic insight into a number of renal diseases, provided by probing functional consequences of disease-associated gene and protein changes as they are identified in patient populations. Mechanistic data, together with multiplexed biomarker profiling, provides powerful insight into the causes of acute and chronic kidney disease. These insights are used to guide discovery of novel and targeted drugs for best outcome in therapy of stratified and well-defined patient groups.

The development of novel *in vivo* experimental models of aHUS is also allowing unparalleled opportunities to improve patient care by defining the triggers of aHUS and allowing the development of novel complement therapeutics for aHUS and C3G. The exploitation and transfer of these drugs into the clinic, including their development for use in kidney transplant models are key aims for the coming years.

The work of the research group extends beyond kidney disease to include diseases of other organs, such as the eye, where complement plays a causative role. Drug discovery and development initiatives are carried out in collaboration with both internal and external academic and industry partners.

2. Service Activity

Referrals to the National aHUS Service have been increasing year on year. The annual referral numbers to the service in each of the last 3 complete financial years are summarised in *Figure 2*. During the same reporting period, the number of patients treated with eculizumab for incident cases of aHUS remains broadly unchanged. Use of eculizumab in prevalent patients with aHUS as part of pre-emptive treatment at time of transplantation has decreased and reflects the backlog of patients who were prohibited from transplantation before eculizumab was available.

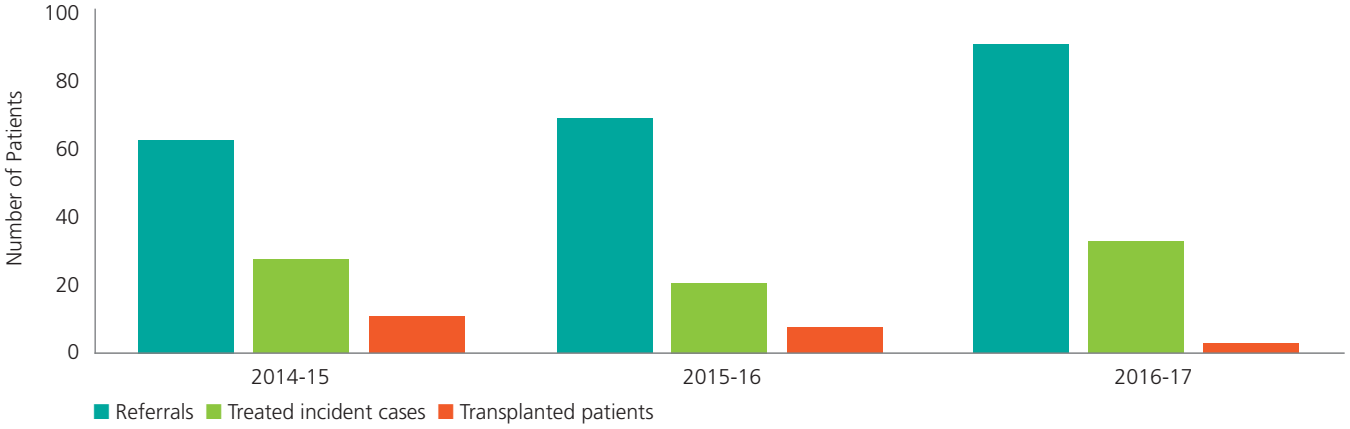


Figure 2 ***National aHUS Service annual activity***
Bar chart shows number of patients referred to the National aHUS Service, the number of patients recommended for treatment of incident cases of aHUS with eculizumab and the number of prevalent aHUS patients receiving pre-emptive eculizumab at time of transplantation in each of the last 3 complete financial years.

In this first reporting period (June 2016 to March 2017) of the fully commissioned service, the National aHUS service has received 70 referrals for Eculizumab in patients with a potential diagnosis of aHUS. During the same reporting period, Eculizumab was recommended in a total of 32 patients *(Figure 3)*. Of these patients, by the time of reporting (Oct 2017) only 20 patients were receiving Eculizumab (Figure 4), of these 65% had a complement genetic mutation.

Eculizumab was withdrawn in a total of 12 patients that had been initially recommended Eculizumab during this reporting period. Three patients remained dialysis-dependent and a decision to stop eculizumab was made. Of the remaining nine patients, in whom there was evidence of renal recovery the most common reason for stopping was subsequent confirmation of STEC-HUS.

A total of 5 patients were recommended for pre-emptive treatment with eculizumab at time of transplantation (*see section 3.2*). A total of 33 patients referred were not recommended for eculizumab.

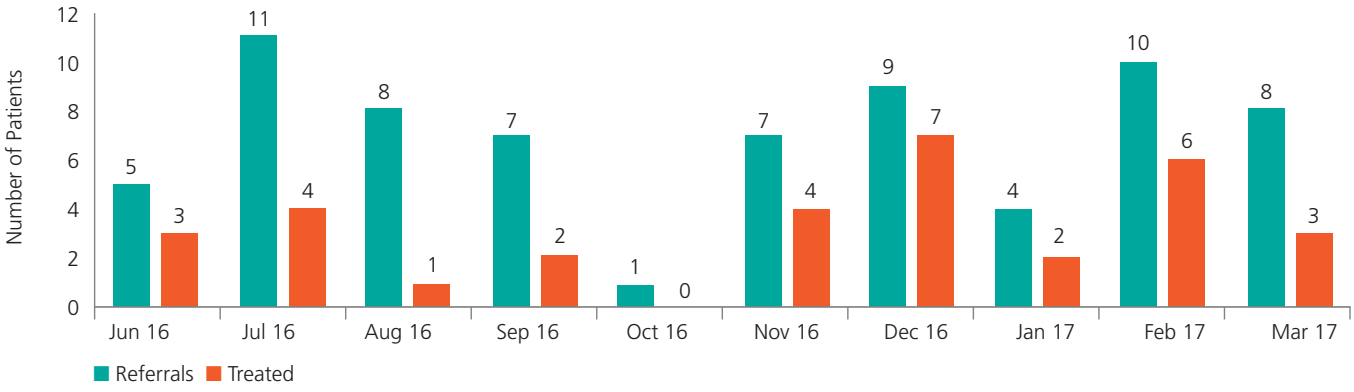


Figure 3 ***National aHUS Service monthly activity***
Bar chart shows number of patients referred to the National aHUS Service and number of patients recommended for treatment with eculizumab in the reporting period from June 2016 until March 2017.

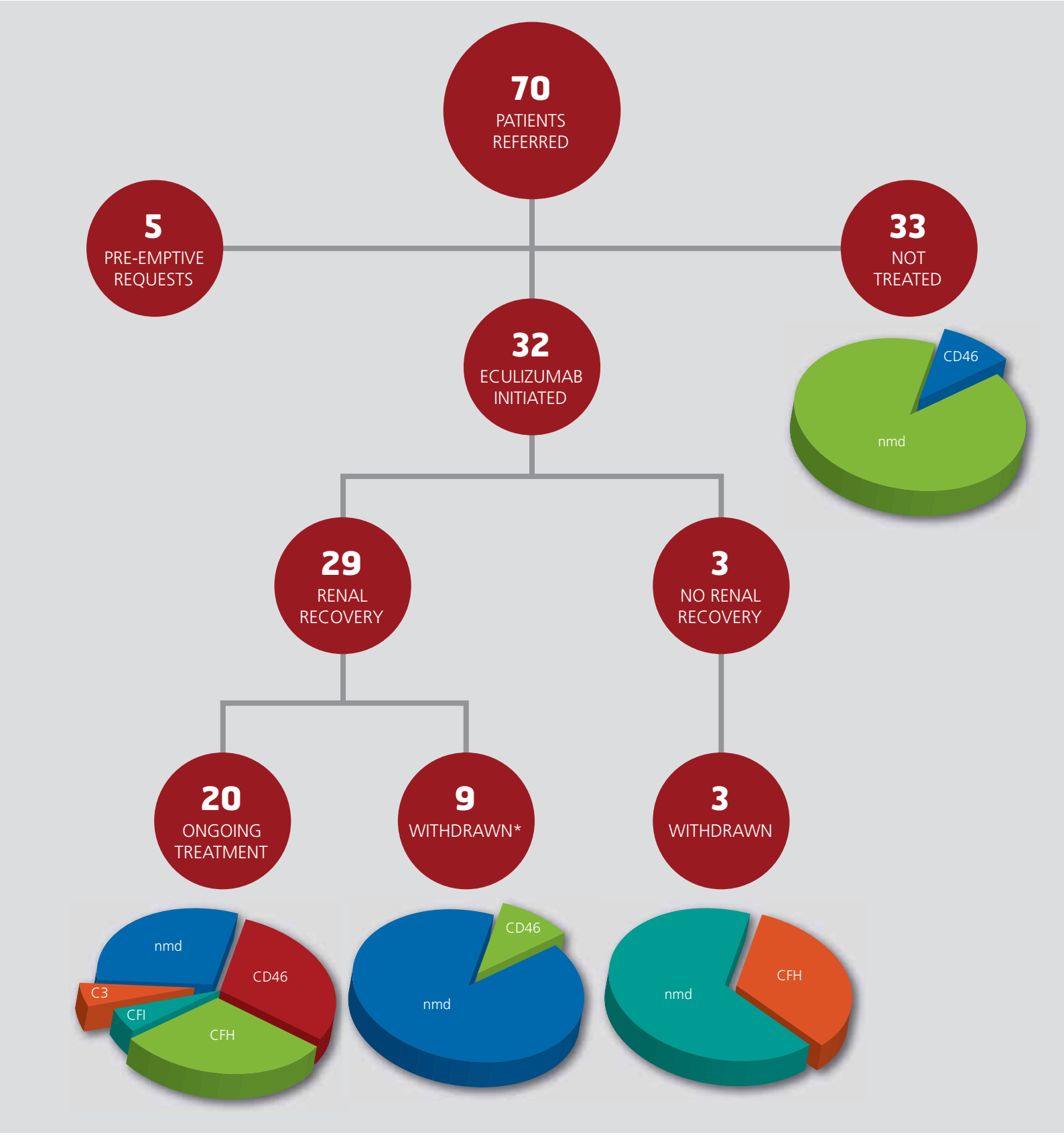


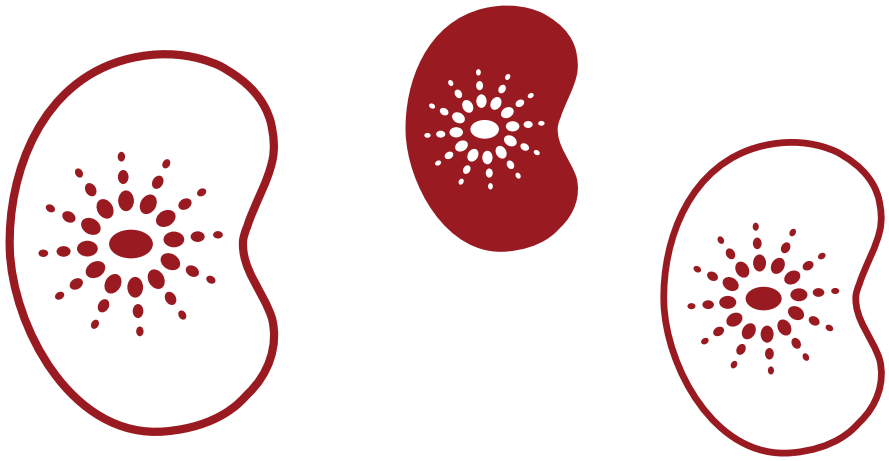
Figure 4 ***National aHUS Service activity from June 2016 until March 2017***
*Following initial assessment of 70 patients with a possible diagnosis of aHUS, Eculizumab was recommended in 32 patients. Three patients remained dialysis-dependent after 3-months treatment with Eculizumab. *Eculizumab was withdrawn in a total of 9 patients who had recovery of renal function – reasons for withdrawal were confirmation of STEC (4 patients), probable STEC (1 patient), subsequent sepsis – clinician choice (1patient), patient choice (1 patient - with CD46 mutation), spontaneous recovery prior to first dose of eculizumab and patient death (1 patient – not eculizumab related). Twenty patients remain on eculizumab. All patients receiving Eculizumab were screened for complement genetic mutations. The proportion of patients with a mutation in each of the genes (CFH, CFI, CD46 and C3) for each treatment arm is shown in the pie charts [nmd = no mutation detected].*

3. Performance Analysis

The service measures its performance across the NHS outcomes framework domains and quality indicators, detailed below.

Quality Requirement	Threshold	Method of Measurement	Consequence of Breach
Domain 1: Preventing people dying prematurely			
Zero avoidable deaths in patients with a diagnosis of complement mediated aHUS (as per current diagnostic criteria)	Zero deaths	To be notified to the commissioners including HSS national team within 24 hours	To be addressed in annual service audit meeting
Domain 2: Enhancing the quality of life of people with long- term conditions			
All patients with aHUS who are eligible for renal transplant will be listed for transplant	100% of patients on transplant waiting list	Annual audit	To be addressed in annual service audit meeting
Publish an annual report from the aHUS registry	Report published to agreed timetable	Report received by NHS England	To be addressed in annual audit meeting
Domain 3: Helping people to recover from episodes of ill- health or following injury			
To provide advice to provider centres within 24 hours of request on treatment	90%	Annual audit report	To be addressed in annual service audit meeting
Written protocols agreed with units	100%	Annual audit report	To be addressed in annual audit meeting
Domain 4: Ensuring that people have a positive experience of care			
Achieve 90% data completeness of the aHUS register to which referring units are mandated to supply data	90%	Annual audit report	To be addressed in annual service audit meeting

Table 1 ***National aHUS Service - Quality Indicators***



3.1 Domain 1: Preventing people dying prematurely

Zero avoidable deaths in patients with a diagnosis of complement-mediated aHUS

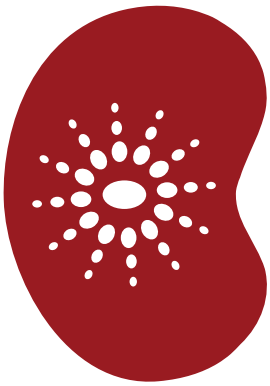
No patient died of aHUS in England

As of the 31st March 2017 there were one hundred and twenty one patients receiving Eculizumab under the shared care of the National aHUS Service.

During the year four deaths were reported to the service, however the National aHUS Service was not notified within 24 hours of the deaths.

Following notification of the deaths the patients were discussed at the clinical multi-disciplinary team meetings. A formal mortality and morbidity meeting was held once more information was available from the local team. We concluded that the four patients who died were treated for aHUS appropriately based on the information available at the time.

No deaths occurred directly as a result of aHUS.



Challenges in the delivery of Domain 1

1. Completeness of data at the time of referral. Complete data is critical for the accurate initial diagnosis and treatment recommendation. Sufficient data is not always provided at the time of referral. This is being addressed by increasing interaction between the National aHUS Service and referring clinicians, improved documentation and implementation of the shared care protocol. Regular review of patients who start treatment is now standard practice.
2. Completeness of follow up data. This is required to decide on the requirement for ongoing treatment. This is being improved by clearly defining the responsibilities of local clinicians within the shared care protocol, increased contact with local units and automated collection of data through the UK Renal Registry.

Infection Prevention in patients receiving Eculizumab

We also recognise that there is a risk of morbidity and mortality due to the risk of infection in patients receiving eculizumab. All clinicians are informed about the risk of meningococcal infection when their patients are approved for treatment. Meningococcal vaccination is required prior to the initiation of Eculizumab treatment and long term antibiotic prophylaxis is recommended. One of the challenges has been obtaining titres post vaccination to monitor the vaccination response. This will be discussed further in domain three in the report.

Medical alert cards *(Figure 5)* have been produced for the patients receiving treatment to ensure they receive appropriate care when seeking medical treatment. The cards also contain the service website and contact details.

Familial risk of aHUS

We are now able to offer genetic testing to all relatives of aHUS patients who carry a genetic mutation to identify those who are at risk of developing the disease in the future. Early recognition of the disease is important in preventing the morbidity and mortality associated with aHUS. At risk family members are provided with a medical alert card *(Figure 6)*, stating that they are at risk of developing aHUS and indicating where information can be found on our website.

Recommendations:

- Quarterly Mortality and Morbidity meetings.
- Develop a Mortality and Morbidity proforma.
- To continually review our processes for data collection and completion.
- Ensure our meningococcal prevention and monitoring is accurate with information available on the National aHUS Service website.
- Advise all at risk relatives are counselled about the risk of disease and offered genetic screening.

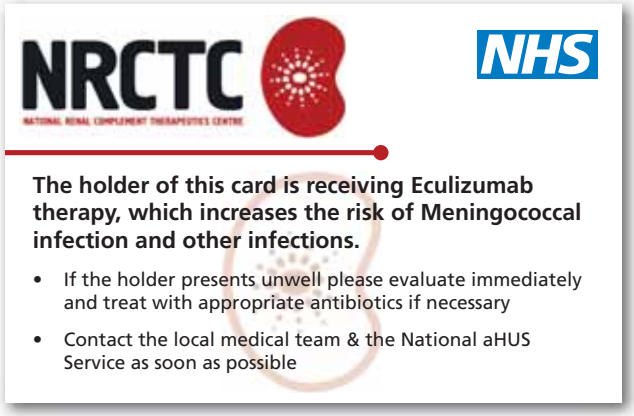


Figure 5 ***Patient-held alert card - meningococcal risk***

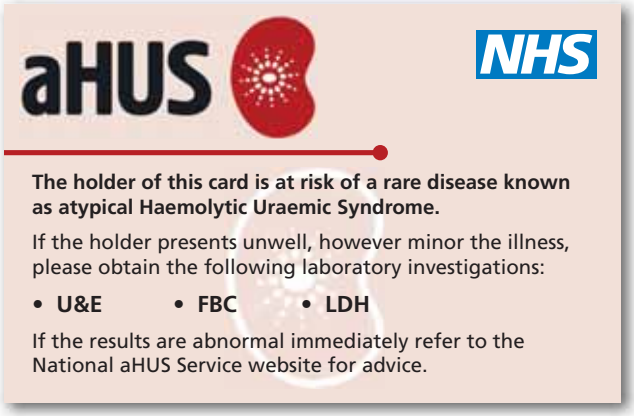


Figure 6 ***Patient-held alert card at-risk of developing aHUS***

Figure 7 ***Access to Eculizumab*** *- emergency referral process is found on www.atypicalhus.co.uk/emergency-referrals/*

3.2 Domain 2: Enhancing the quality of life of people with long term conditions

All patients with aHUS who are eligible for renal transplant will be listed for transplant

We achieved the target of 100% of patients with aHUS who are eligible for renal transplant will be placed on the transplant waiting list. All aHUS patients eligible for renal transplantation referred to the National aHUS Service have been authorised for pre-emptive Eculizumab as per our transplantation protocol.

There were 30 patients on the pre-emptive list for transplant on the 1st June 2016. This is a list of patients who are at risk of their disease recurring after transplantation and for whom pre-approval is given for Eculizumab to be administered at the time of transplant or as a response to evidence of disease recurrence. Three patients were transplanted between 1st June 2016 and 31st March 2017. In this same period, a further five patients were listed for transplant and approved for pre-emptive Eculizumab in the event of being transplanted.

Recommendations:

- To commence conversations about transplant with the referring team at the earliest juncture
- Bi monthly MDT reviewing patients placed on the pre-emptive list

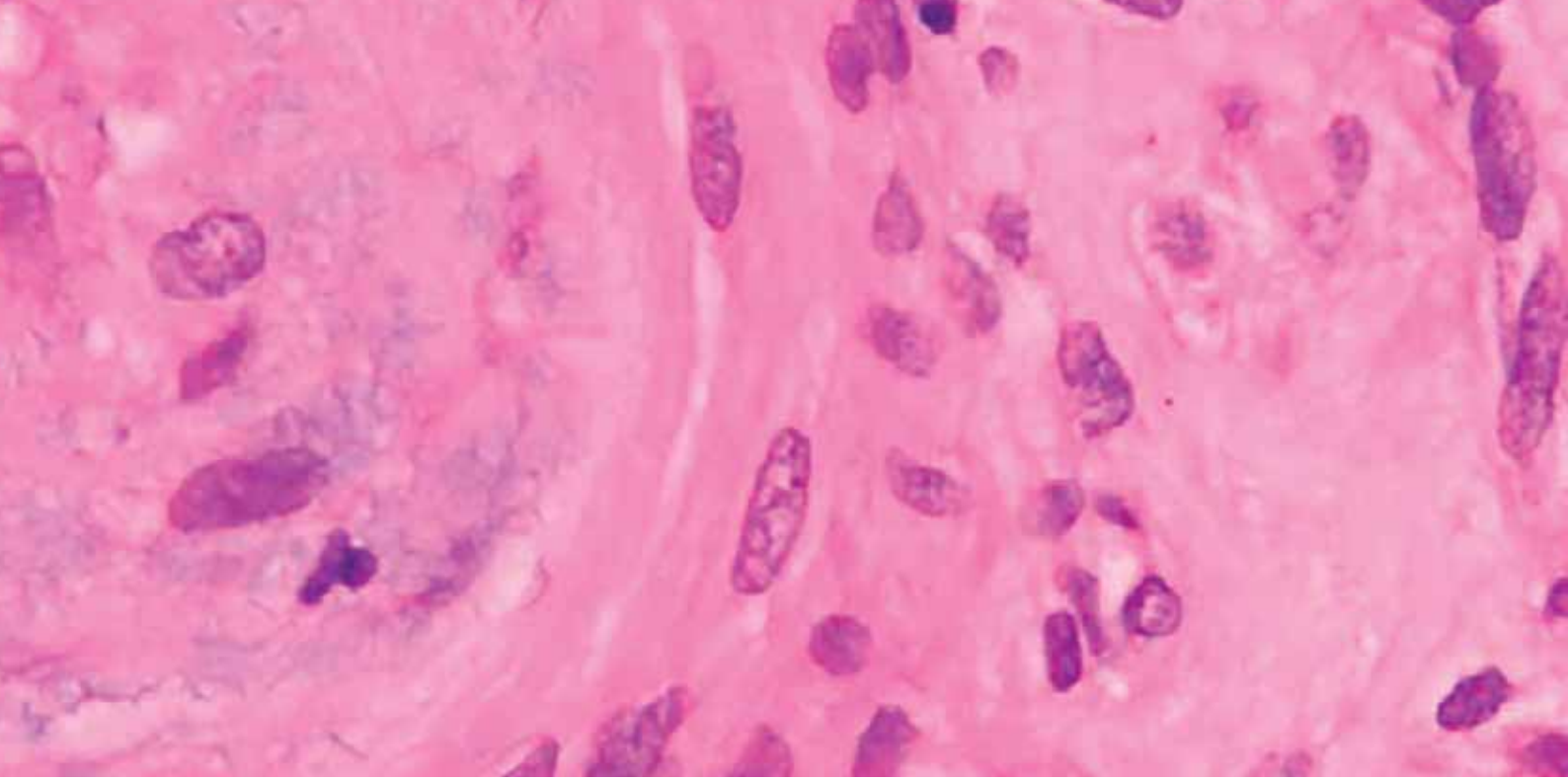
3.3 Domain 3: Helping people to recover from episodes of ill-health or following injury

To provide advice to provider centres within 24 hours of request of treatment

We provide a 24 hours, 7 days a week consultant led on call service. The referral process *(summarised in figure 7)* has been shared nationwide in newsletters and at national meetings to the medical community.

Seventy patients were referred to the service in the first year of commissioning, with a possible diagnosis of aHUS. We achieved 98%, for the quality indicator of providing advice to the referring units within 24 hours; the standard required is 90% *(Figure 8)*.

The only referral which did not receive advice within 24 hours was due to the referring clinician emailing the service over a weekend and not telephoning the on call clinician. The referring physician recontacted the service the following week.



Written protocols agreed with units

Written shared-care protocols were developed following an extensive consultation process with our stakeholders and approved by NHSE during Quarter 4. These were sent to all clinicians initially who have patients currently receiving treatment. This included twenty two for this reporting year, ten patients were no longer receiving treatment at this time. To date we have had fifteen protocols returned for this reporting year, one unit has refused to return the protocols resulting in an overall return rate of 68% *(Figure 8)*. Follow up letters are sent to clinicians not returning the shared – care protocols within an eight week time period.

Recommendations:

- Service website with clear referral instructions and contact details for the service
- All physicians will be sent shared – care protocols at the time of referral

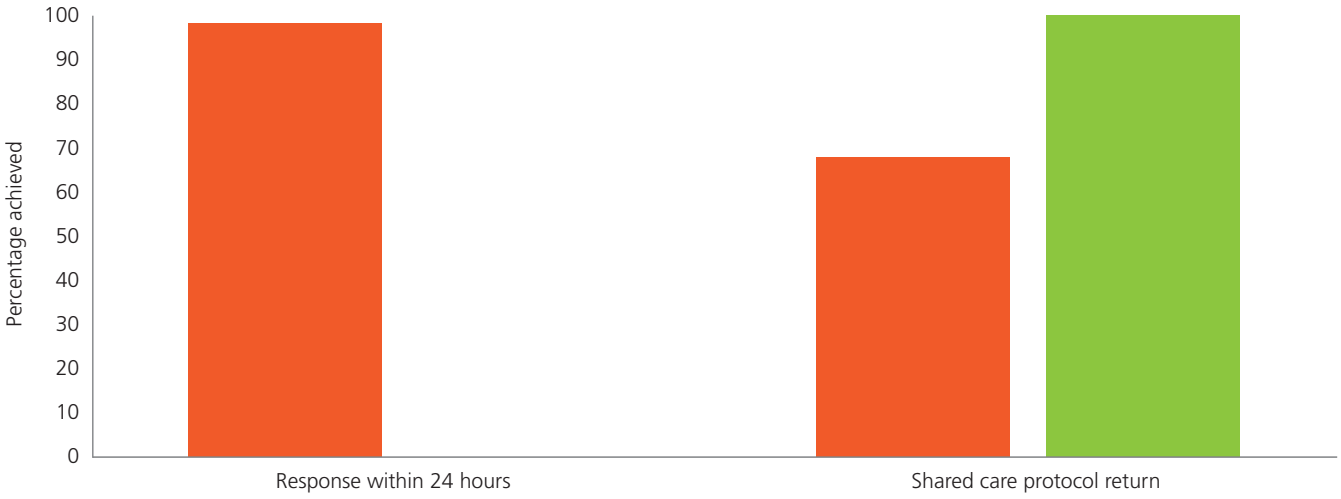


Figure 8 ***Concordance of giving advice and return of shared care protocol*** *- Following referral for eculizumab in a patient with a potential diagnosis of aHUS, we were able to provide a response within 24 hours in 98% of cases. The shared care protocol was sent out to referring units who had a patient receiving eculizumab. Clinicians have agreed to the protocol in only 68% of cases. One single unit has not agreed to the protocol – clinicians have agreed to the protocol in 100% of cases (green bar) if the one single unit is excluded from reporting.*

3.4 Domain 4: Ensuring that people have a positive experience of care

Achieve 90% data completeness of the aHUS register to which referring units are mandated to supply data

Our key aims within this domain are to ensure that an accurate diagnosis of aHUS is made and to protect patients from treatment-related harm. A diagnostic checklist is forwarded to the referring clinician for completion to ensure data completeness.

There are five categories of data we measure the standard of data completeness against for those patients approved for treatment:

- Referrals for genetic testing
- Initial vaccination titres
- Vaccination against Meningococcal Infection
- Shiga Toxin E. *Coli* (STEC)
- ADAMTS13

The results of the data collected from patients requiring genetic testing, vaccination, STEC testing and ADAMTS13 are shown in *Figure 9*. Data collection in three of the five categories achieved the 90% standard.

Genetic Referrals

All patients referred to the service are offered genetic testing, which is carried out unless an alternative diagnosis has been reached. Therefore genetic testing was completed for fifty eight patients of the seventy referred to the service. All patients receiving eculizumab had genetic testing.

Meningococcal Prevention

All patients who commenced treatment received meningococcal vaccination (ACWY and BEXSERO®).

The poor result for the vaccination titres is largely due to one unit refusing to perform titres on their patients. For this reporting period this equates to 30% of the new patients vaccinated. The overall performance was 85% (light grey bar) if this one single unit is excluded from reporting.

STEC

Investigations to detect STEC are requested on all patients unless it is not clinically indicated; this ensures that patients with "typical" HUS (self-resolving) are not subjected to potentially life-long Eculizumab treatment. Thus six patients were excluded from the data set as STEC testing was not clinically relevant. STEC testing was therefore requested on the remaining twenty six patients.

ADAMTS13

An ADAMTS13 result was available for twenty eight patients. In four cases it was not deemed necessary as three were children and one was an existing patient with a known genetic mutation who had been referred to the service in 2002. According to the KDIGO consensus guideline, an ADAMTS13 result is not necessary prior to commencement of Eculizumab in paediatric patients because of the rarity of TTP in this population, unless family history is suggestive.

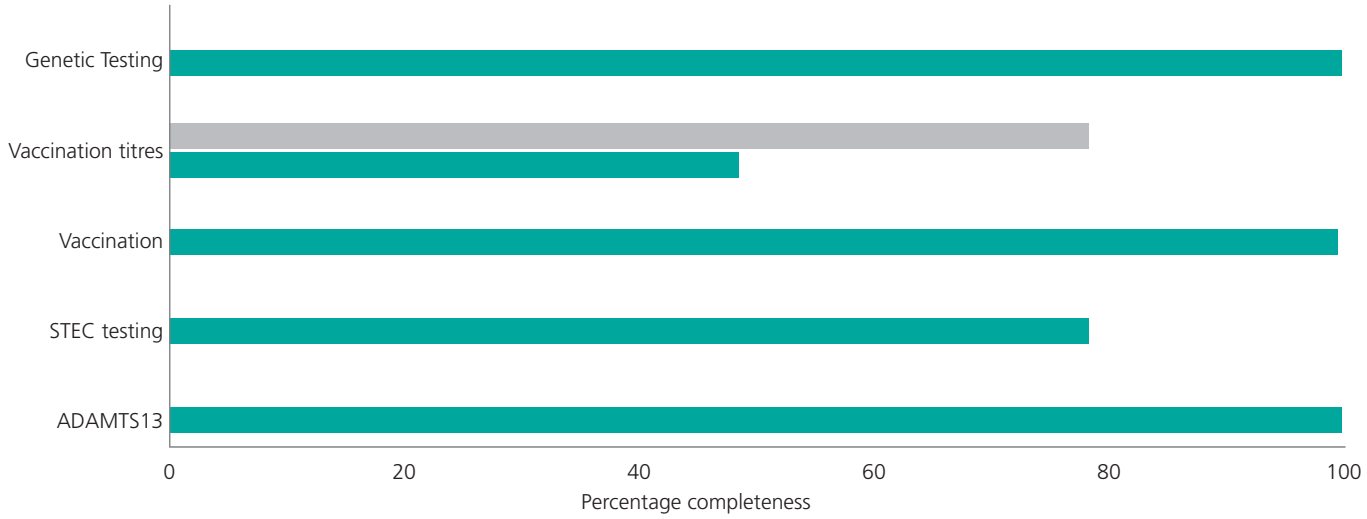


Figure 9 ***Data completeness of the aHUS register.*** *Performance has been measured against 5 categories of data. Data for genetic testing, vaccination and ADAMTS13 was above the 90% quality standard. One unit has not agreed to the measurement of vaccination titres and largely explains the poor performance in this domain – The overall performance was 85% (light grey bar) if the one single unit is excluded from reporting.*

During the first year of our service our STEC results have improved as we have developed processes for following up results. The improvement in STEC testing from Quarter 2 compared to Quarter 4 is shown in *Figure 10*.

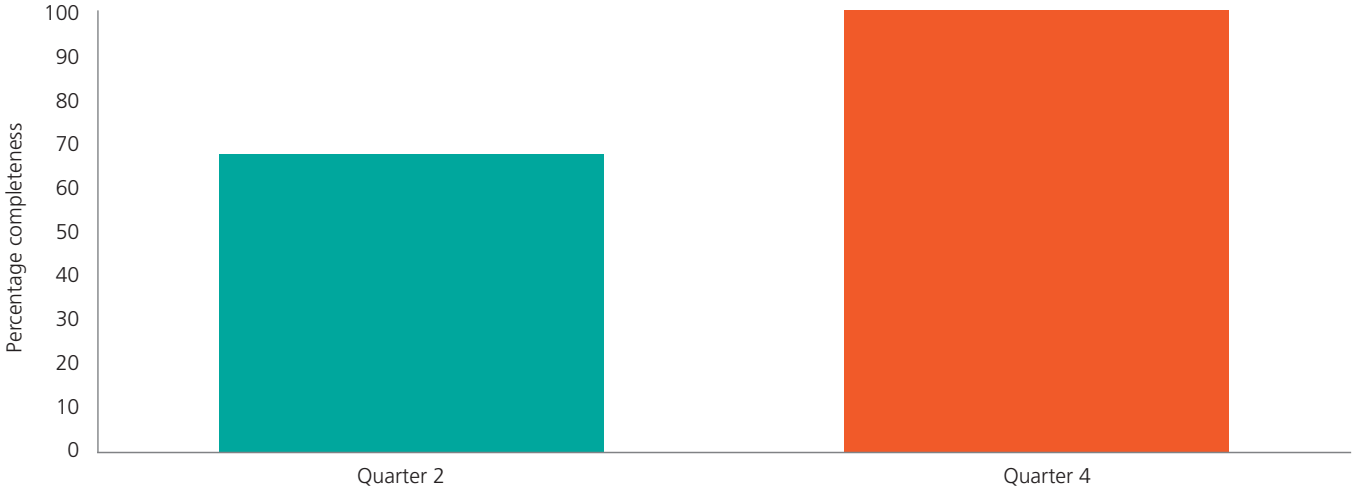


Figure 10 ***Improved concordance of STEC testing during reporting period***

Patient Engagement

In addition to the above set standards for patient experience, our team have been very active in eliciting the views of our patients, keeping them informed of our service developments and producing patient information.

A patient survey was performed in December 2016, which generated a response rate of 46.2%. The patients were asked a range of questions about their disease knowledge and that of the clinicians who care for them locally. Patients were also asked to respond to a range of questions regarding improving patient experience.

One of the key findings of the survey was that our patients would like to receive a newsletter from the National Service; our first newsletter was published in February 2017.

Hand held records are also being developed in order to empower our patients to take ownership of their care. These are discussed further in the report.

Out Patients Clinics

In Quarter 4 we commenced fortnightly outpatient clinics; each patient is offered a one hour appointment which may be increased to two hours if they are accompanied by other family members. Five patients were reviewed in Quarter 4.

Recommendations:

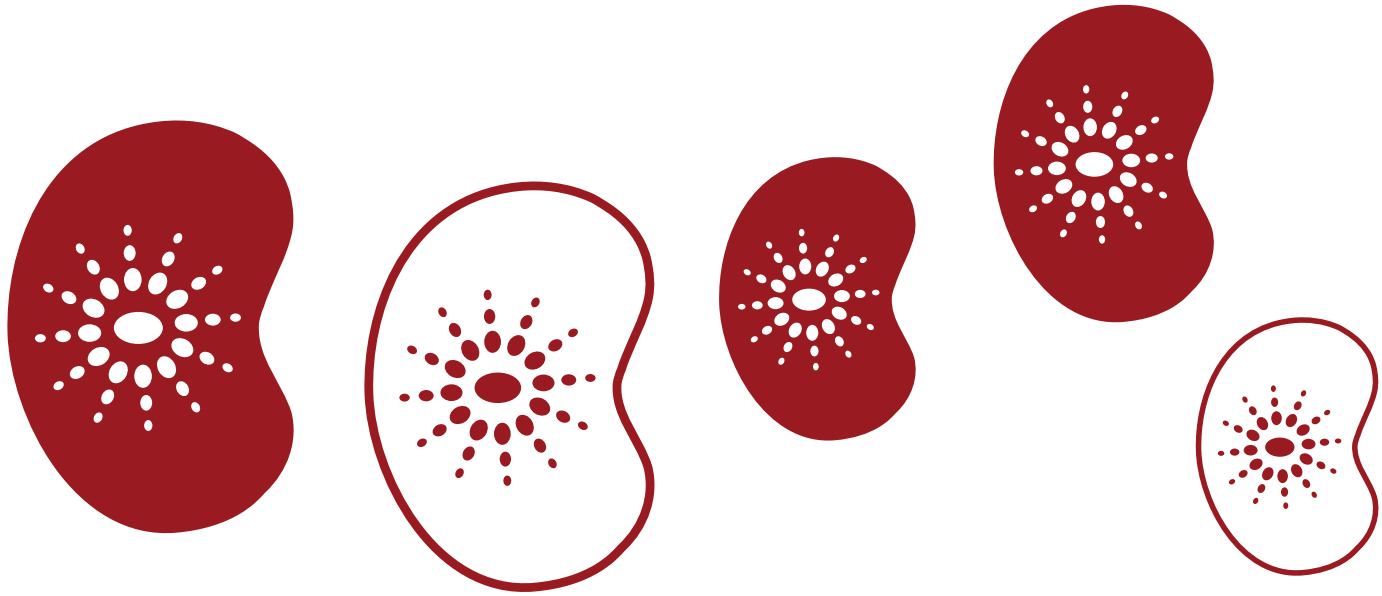
- Meeting to be arranged between National aHUS Service and Professor Ray Borrow from the National Meningococcal reference laboratory to discuss results of meningococcal vaccination titres in cohort.
- Meeting to be arranged between National aHUS Service and Dr. Claire Jenkins from the national gastrointestinal bacterial reference unit.
- Review at two weeks for outstanding results on all new patients.
- MDT to review all new patients at one, three and six monthly thereafter.
- Specialist nurses to offer to complete consent for the 100,000 Genome project either face to face or obtain telephone consent.
- Nurse telephone consultations.
- Nurse led clinics for local patients.

4. Achievement of Performance Targets

The results compiled in this report are not for a complete financial year and encompass the activity of the National aHUS Service from the 1st June 2016 to 31st March 2017. The performance targets are summarised in table 2.

Quality Requirement	Threshold	Percentage achieved
Domain 1: Preventing people dying prematurely		
Zero avoidable deaths in patients with a diagnosis of complement mediated aHUS (as per current diagnostic criteria)	Zero avoidable deaths	Zero avoidable deaths
Domain 2: Enhancing the quality of life of people with long- term conditions		
All patients with aHUS who are eligible for renal transplant will be listed for transplant	100% of patients on transplant waiting list	100%
Domain 3: Helping people to recover from episodes of ill- health or following injury		
To provide advice to provider centres within 24 hours of request on treatment	90%	98%
Written protocols agreed with units	100%	68%*
Domain 4: Ensuring that people have a positive experience of care		
Achieve 90% data completeness of the of the aHUS register to which referring units are mandated to supply data	90%	85%*

Table 2 ***National aHUS Service – Performance during reporting period from 1st June 2016 until 31st March 2017.*** *We met the performance targets for domains 1 and 2. Two standards were not met - *these standards would be met but for the failure of one unit to sign a shared care protocol or check vaccination efficacy.*

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4.1 NRCTC Website

One of our key remits is to provide high quality advice to patients and clinicians about aHUS and C3G. We have developed a website **(http://www.atypicalhus.co.uk/)** providing both lay and professional information and advice *(Figure 11)*.

For our patients and their relatives we describe what aHUS is. We describe how we make a diagnosis of aHUS and what the other potential diagnoses may be. We review the treatment options with a focus on complement inhibitory therapy. We explain the risks of infection in patients on eculizumab and highlight the ways in which we minimise risk through vaccination and antibiotic prophylaxis. We indicate how patients can contact our service and obtain a consultation either locally or virtually.

For clinicians the website serves as a portal to access our full range of services as well as providing an up to date summary of complement mediated renal diseases and their treatments. An emergency referrals page **(http://www.atypicalhus.co.uk/emergency-referrals/)** highlights a 24 hour 7 day a week consultant led on call service. It provides a repository for clinicians to download diagnostic checklists, combined laboratory investigation forms as well as shared care protocols.

Figure 11 Screenshot from the website of the National Renal Complement Therapeutics Centre. The website provides information for patients and their clinicians and also the referral pathway for eculizumab [www.atypicalhus.co.uk].

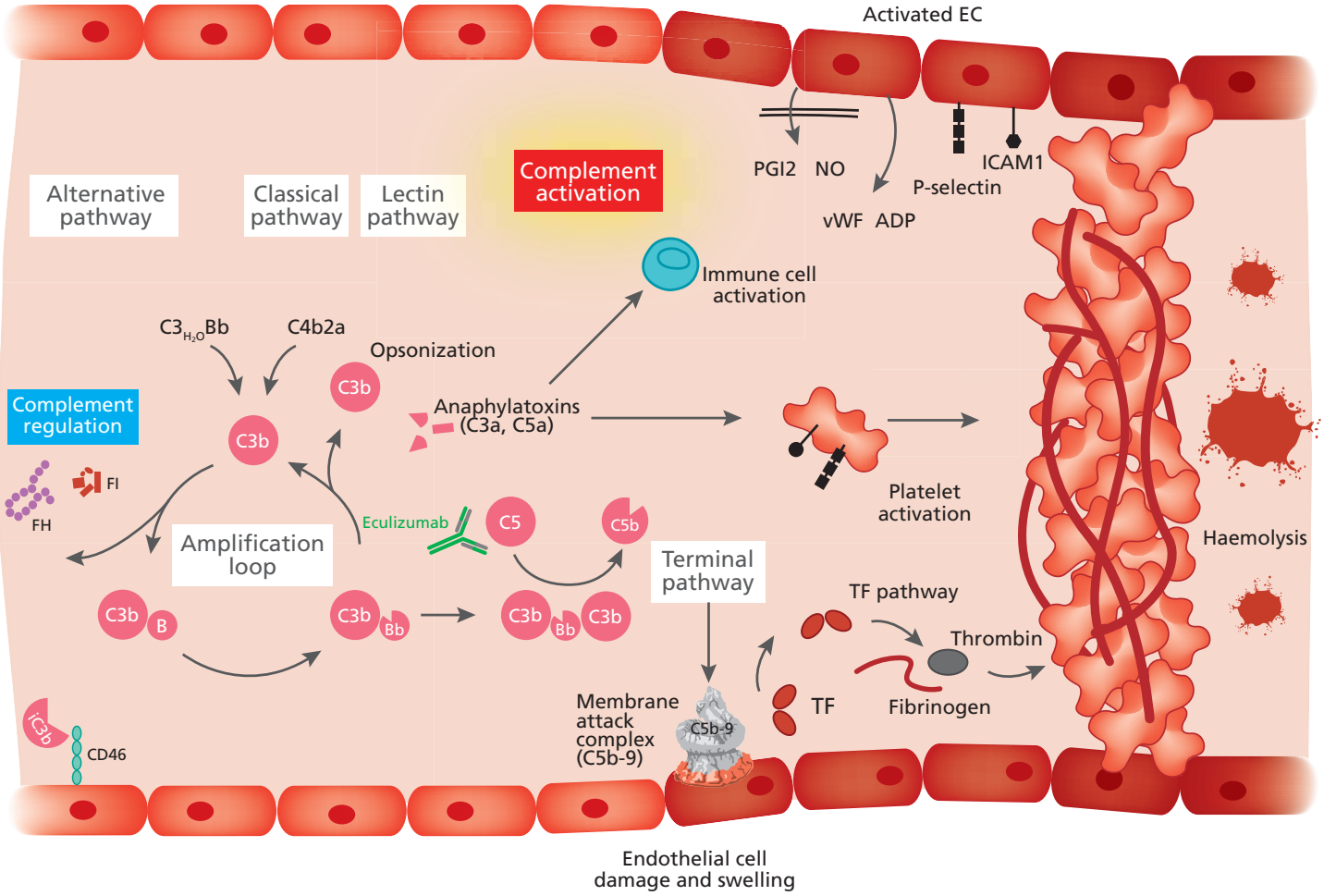
4.2 Patient Handheld Record

To ensure equality of access, in addition to our digital platform, we are creating a written version of our aHUS and C3G patient information. This will be included in our aHUS Patient Handheld Record *(Figure 12)* which will be sent to all our patients on initial diagnosis. In addition to providing information this will act as record of important blood monitoring tests and contact information.

Figure 12 Patient handheld record.


DELL

5. Complement Research at the NRCTC



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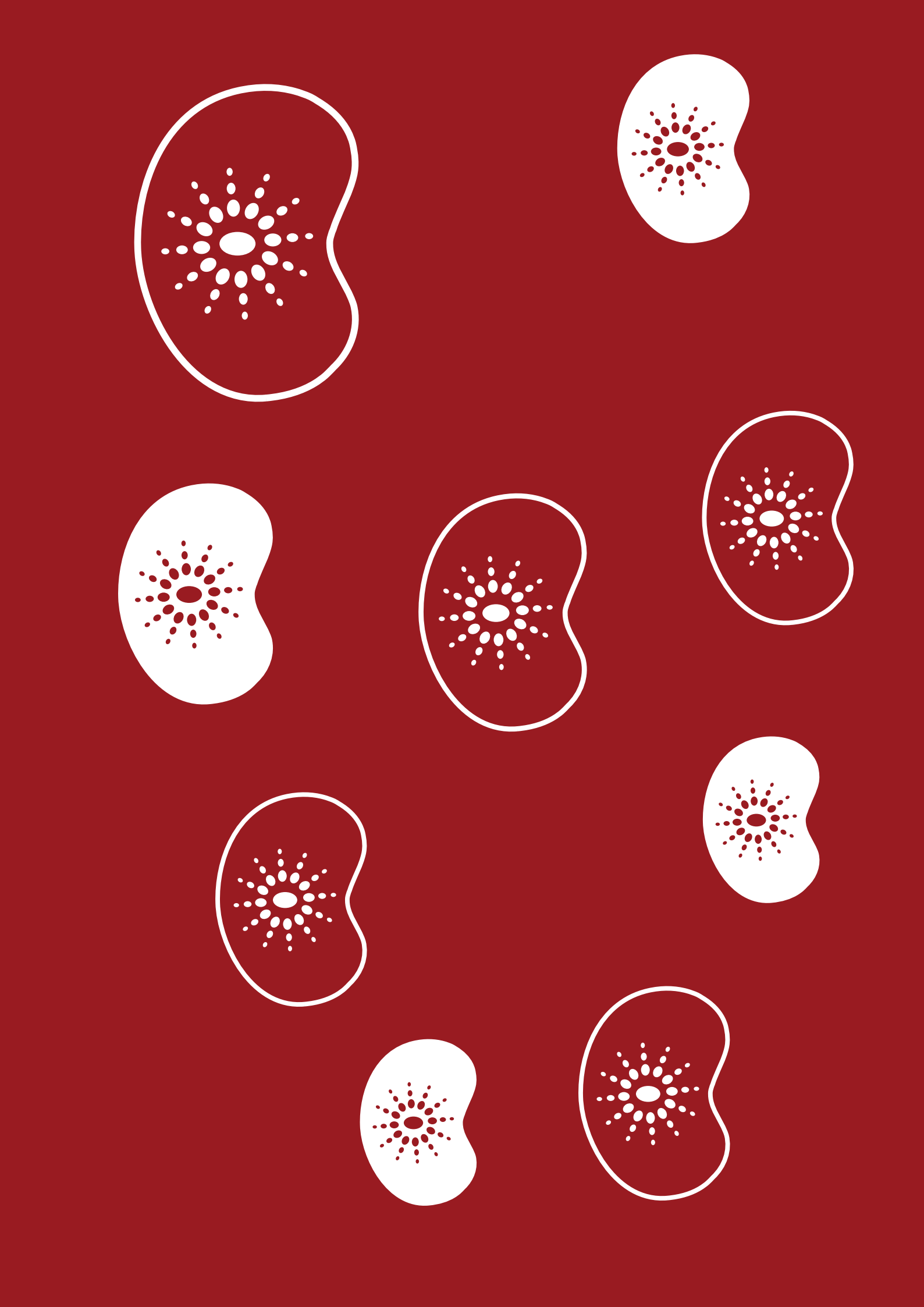

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