A RELUCTANT ADVOCATE

Chapter 1 A change in gear for a Reluctant Advocate

“It’s a “no decision”.

“They said “no”” my wife replied

“No, they said “yes”” I replied

“They said “yes”” She returned

“Yes” I confirmed “but the Minister cannot make a decision now as he wants all done again but this time by NICE, so it is “no decision”

“They” were the Advisory Group for National Specialised Services “affectionately” known as AGNSS (“Agnes”). NICE was the National Institute for Clinical Excellence. The Minister was The Right Honourable the Earl Howe, Parliamentary Under- Secretary of State for Health.

What they were saying “yes” or “no” to was whether a drug called Eculizumab, reputedly the most expensive drug in the world, could be made available in the NHS for the treatment of atypical Haemolytic Uraemic Syndrome, a very rare disease.

It was the morning of 19th January 2012.

The conversation that morning was about something which had become a matter of life or death to our family and therefore marked a moment after which our family’s hitherto reticent involvement in patient advocacy went to a new level and would consume our lives for the next five years.

Chapter 2 Where the heck did that come from?

No one in our family had experience of kidney failure, or so we thought, on 19th January 1997 when our daughter went into respiratory and heart failure in front of our eyes in an old and almost derelict (through under investment), hospital in Manchester; now long pulled down to make way for housing development.

It was a Sunday; the hospital could not afford to open its dialysis unit on a Sunday and so the fluid that builds up when your kidneys stop working cannot be expelled without an artificial kidney machine. So, the fluid builds up in the lungs like someone drowning and the heart struggles against the odds to continue to function.

“Well some got their figures wrong” said the Consultant in the Intensive Care Unit after the renal ward team acted professionally to undo the effects of the treatment which was killing her.

Too much fluid in (kidney patients are often treated for dehydration) not enough fluid out. The Intensive Care Consultant said while showing us an X ray of our daughters’ lungs, the errors in sums had caused one lung to fill up completely and the other was half full, our daughter was now on dialysis to get it out of her. It was the middle of the night but Monday morning, so a dialysis machine could be brought into use to resolve something which earlier the previous day it could have prevented.

We were in the “car crash” scenario, which we now know would be familiar to many of those rare people who have experienced a catastrophic episode of atypical Haemolytic Uraemic Syndrome, or aHUS.

aHUS is very rare although no one knows how many people in the world have survived an encounter with it. Estimates vary between 15000 and 42000. Each year in the UK there will only be around 25 incidents.

Haemolytic and Uraemic are just describing the symptoms of the disease. aHUS patients will experience severe anaemia caused by their red blood cells being destroyed because of uncontrolled clotting in the body's capillaries leave smaller and smaller gaps for the blood cells to squeeze through. The gaps gets so small that the cells explode like a balloon. This is known as haemolysis.

This uncontrolled process seems to happen most frequently, but not exclusively, in the capillaries in the kidney. When it does, it causes the filtration system in the kidneys to become blocked. Once blocked the kidneys are not doing what they should be doing, here is, among many other effects, a build-up of uraemia in the blood a sign that the kidneys are failing to work.

aHUS is not the only disease in which this happens. HUS, the typical version, is more common. It is triggered by E. coli poisoning. The excessive haemolysis is the result of the virus binding to red bloods cells so that the body's immune system targets every cell to get rid of the virus in a form of friendly fire. There are very few incidents of HUS each year, yet it is ten times more likely to happen that the atypical version. Whilst HUS is the result of poor hygiene in food preparation or animal contact, aHUS can be triggered by other factors and aHUS patient's immune response is uncontrolled because of minute inherited defects in the aHUS patient's own immune control system. The controls are needed to stop an excessive and unnecessary immune response to whatever has triggered it.

No one can be sure what triggered the illness in our daughter. At the time she was living in Glasgow when the news was full of a story about an E. coli outbreak in a nearby town in which poor hygiene practices by a local butcher had resulted in E. coli contaminated meat being served at a party causing partygoers to become ill. The youngest and oldest of them dying from kidney failure. HUS was not necessarily something that would have been mentioned.

There were many people in the Glasgow area who were experiencing stomach upsets at the time, including our daughter. But unlike others who recovered quite quickly she did not. In the following six weeks or so her condition deteriorated until eventually a local doctor discovered from a simple blood test that she was in kidney failure.

It did not take long for the Renal Consultants in the hospital that she was hastily referred to, to see from the tell-tale signs in the blood that the cause of the kidney failure was HUS, although by then no evidence of E. coli could be found in any cultures that were taken.

Just what had hit us out of the blue. How could someone who had that summer toured the USA including universities in New York and Bloomington in perfect health now be laid so low near to death.

Although we did not understand much at the time and had no idea then why the doctors were looking for other possible causes pregnancy, AIDS, drug use there was a clue in our family history which we did not know was significant.

Chapter 3- Now where is my tutu?

With the family moto "*Non Offeres" ("Never Volunteer")* going through my thoughts, as I entered the door of 1, Wimpole Street, London on 10 September 2011 little did I know how that day would change my life for the next seven years or more.

Wimpole Street is well-known, and No 1 houses the Royal Society of Medicine in very prestigious surroundings. One of the changes I would experience was that I would now visit many such impressive, famous and historic venues over the coming years.

That day it was just to find out about the need for an aHUS patients organisation.

I had kept my head down when a volunteer was asked for to be the first appointed Trustee of the patient organisation, which we had discussed and had agreed to form.

The first Trustee's role to be elected was that of Treasurer.

"He will do it" I heard as my family volunteered me. I had been a qualified accountant for over 30 years and it was something that could do albeit with no previous experience of a charity accounting.

So "Yeh I will do it" I said.

That was it, that was the start!

The meeting had been called by Professor Tim Goodship, the Doctor who had we had first heard of when our daughter was first ill in that derelict hospital in Manchester, and when advice was being sought on the likely outcome of a transplant with a living donor.

Prof Goodship, as he became, had undertaken genetic tests from our blood samples and had found that my daughter and I had a genetic predisposition to aHUS. That was important for the donor decision.

Now we were in the room with the families of another seven aHUS patients who had experienced aHUS who had answered Prof. Goodship call and had been challenged to become a formal charity with objectives rules and a constitution. To say there was a reluctance by all to do so would be an understatement.

As the meeting progressed it had become clear to us that such a group was essential to meet the National Health Service's demands to be able to provide the patient case when its committee met to evaluate the case for eculizumab to be used for aHUS in England. None of us had done anything like that before, but as our family came to realise that if a "box had to be ticked" then "tick it we would" if it meant that our daughter could have a successful transplant at last. Some said that "if they had to stand in a corner with Tutu singing "God Save the Queen" to get access to a clinically effective treatment, then so be it".

A charity was created but only members from five of the seven families attending were prepared to join in. It makes you think that there estimated that were over 150 families affected by aHUS at that time and now the burden fell to just five. It soon became four as one of those five families had second thoughts after the meeting and resigned, although the reasons for doing so seemed to be odd.

That is what is like in charities, they are often run by a disparate group of strangers bound together with a common aim, which in our case was to convince the cash strapped NHS to fund treatment for aHUS patients with a drug reputed to be most expensive in the world. And there was less than a month to get started before the first meeting with the NHS was to be attended. If things were to be done that quickly we thought it could all be over with by Christmas.

We also knew enough about each other to be aware that we lived in all corners of England and had no resources to do anything. To fund our ourselves we needed to be a legally registered charity.

Serious consideration of the “Tutu option” now seemed to be the better alternative!

Chapter 4 Hurry up and wait

It did not take long to realise the meaning of the saying “Hurry up and wait” as far as the NHS is concerned. “To be done by” dates for third parties, which aHUSUK the name of the charity formed in the Wimpole St had become, were fixed in stone whilst dates for the NHS were flexible.

So aHUSUK’s first meeting with the Advisory Group for National Specialised Services (AGNSS) was held on 31 October 2011 not early in October as was thought. Two trustees attended the meeting, the Chair of the charity and our daughter. The three-hour meeting was held to discuss the scope of Eculizumab for aHUS not to evaluate it. The evaluation meeting was now predicted to held in June 2012, so much for it being over by Christmas 2012, and eight months would be needed just to get ready for the Group to evaluate the drug.

The meeting was also the first opportunity to meet some of the members of the Group as well as the people from the NHS who managed the whole process and who we became reliant on as we learned what was needed as none of us had done anything like this before.

It was also the first encounter with employees of Alexion and their consultant advisors.

My daughter’s recollection was how welcoming and hospitable everyone was with refreshments laid on for early starting meeting finishing at lunchtime. As she was the only one who living with aHUS on dialysis, she was asked to give a brief introduction of her experience. Perhaps the most telling illustration was that in front of her was a small cup of water which was still full. Although everyone had been kindly offering her drinks before the meeting and in breaks, she said that that cup represented her total fluid intake allowance for

the day. The food laid on had also contained too much salt and potassium related items for someone reliant on dialysis. These are the kind of day to day challenges that, that those not familiar with dialysis struggle to understand. In such simple ways the patients voice was already resonating.

Later, the Chair of AGNSS spoke to her and commented on how well she looked despite fourteen years of dialysis and asked whether she would wish to have an eculizumab supported transplant. “In a heartbeat” was her immediate response “…as it would mean Freedom”.

The meeting also introduced the principles on which the decision-making frame had been designed with the Patients needs had been out front and centre. It was a decision-making process that had been developed specifically for health technologies for those with rare and complex diseases diseases* which met pre-set criteria of which there had to be less than 500 patients affected in England. Although no one really knew the exact number there were fewer than 200 aHUS patients in England.

The underpinning principles were:

Societal value
Best practice
Sustainable Cost
Health Gain
The framework developed from these principles required evidence to show:

Does eculizumab work?

Is it the best way of delivering the service?

Is it a reasonable cost to the public?

Does it add value to society?

For each of these criteria were set, which for each would determine if they were met. But the Group would take a holistic view across all criteria.

aHUSUK believed most of the criteria would meet but the “reasonable cost “, when eculizumab was reputedly the most expensive drug in the world, was going to be a challenge even though every aHUS patient would think it was reasonable.

The trustees left the meeting with the task of providing a “Patient Submission” by 30th January 2012. No firm format was given for it as the Group were still consulting organisations who had previously gone through the process in the past to come up with a novel way of doing it. Given the lack of resources and experience that aHUSUK had, it was likely that we would be given access to consultants to help with the submission.

The time it was going take depended on the NHS, so the completion date was going to slip!

This was just the start.

Chapter 5 Much ado to do nothing

The AGNSS journey had begun and it was to be aHUSUK's key task and focus for several months.

At the same time the demands of being a charitable organisation with objectives were also to be addressed.

None of the trustees had any knowledge or experience of running a charity although the trustee board possessed a range of skills and professional backgrounds. The charity had to be registered with the Charity Commission if it needed funds, and for that it needed a bank account.

It also needed members, the charity was an association (the membership decide what is done) not a Foundation (Trustees Decide). We needed to hold an inaugural meeting and soon. Members were also needed to make the AGNSS review more inclusive and informed, and for that the charity needed to be known about. It was too simple to expect the NHS to let us know who the aHUS patients were, and we soon got to know that the rights to personal anonymity superseded the right to know how their illness could be treated and to help with getting it.

At this point most aHUS patients knew nothing about what was happening to help them. Sadly, neither did many of those whose job it was to care for them.

Not all patients wanted to be treated either and we soon found out that not everyone shared the desire to leave a life of dialysis. One of the trustees thought that and resigned as he could not support an application for aHUS patients to receive eculizumab. Charities for health action are frequently created by disparate strangers with varying views. We went our separate ways.

aHUSUK objectives, as all health charities seemed to do, included raising **awareness** of aHUS and getting better **understanding** of the disease (something individually even we rapidly needed to do) as well as provide **support** and **help** to those affected by aHUS. For the latter we saw having unfettered access to eculizumab as the main way we could support and help. Juggle the key words around **a**wareness **h**elp **u**nderstanding and **s**upport and result is aHUS and that becomes the underlying theme for an aHUSUK website. Online visibility was almost mandatory for a charity ours was in the process being developed by me, iT and finance often went hand in hand back in the day! Computer skills had to be learned and quick.

We needed a logo and had not got professional design skills not could we afford to go to design consultants. It had to be home made and thought had to be given to it as it had to represent our disease and purpose. It was left to me. The logo I developed was based on a double twisted mobius band which resulted in three sections representing the triad of aHUS symptoms, anaemia, clotting and kidney failure. The band was also given the colours of the rainbow to symbolise our optimism for the future. The website had a backdrop of blue sky to conclude the feeling of “hope” that aHUSUK was to give. That exhausted my design capability! It would have to do.

Although we were beginning to think as a large charity; and, with a website creating an image and perception of aHUSUK to back it up, who would really know what was behind it all.

The key difference for us was that large charities, although were governed by un paid trustees like us had paid employees to do the work. In aHUSUK trustees did the governance and all the work for no payment. No wonder the reluctance.

Years later a blog appeared on aHUSUK’s website which contrasted what we had to do compared to other established charities

"Very few people would know about *Naglazyme****, $485,747 annual cost per patient, used to treat mucopolysaccharidosis type VI, which is better known as Maroteaux-Lamy Syndrome. In the UK the patients are represented by the MPS Society which has 12 trustees, interesting to see they are funded among others, by three pharmaceutical companies and employ 13 staff in dedicated office accommodation. MPS patients require the third most expensive drug too.***

aHUSUK has four unpaid trustees who have had to do much the same as the MPS Society with some of their out of pocket expenses for conferences and meetings found from an unconditional grant from Alexion."

I will come to funding of aHUS charities later.

With the splendid efforts of our Secretary we became a registered charity and I got it a bank account. Now we not only had to comply with registration rules and responsibilities but the job of accounting for expenses and complying with financial reporting regulations was to begin. All required time whether the charity was doing things or not. As it was there was much left to do and we had only got to Christmas 2011.

Chapter 6 “It’s BLOODY scary!” An authentic aHUS Patient’s Voice

By Christmas 2011 nothing had been heard from the NHS about what format the patient group evidence would take. But work had begun.

There were two strands of research already taking place

- Although for some of aHUSUK we had not seen another aHUS patient until the first aHUS patients conference which had been held in Newcastle back in June (and which led to the creation of aHUSUK) it was evident from those attending that conference that there was a typical aHUS patient but there was a “spectrum” to describe.
- Similarly, there were treatment outcomes which were different and more extensive than just being on dialysis. Dialysis itself would not come alone and those living with it would encounter complications and debilitating conditions in time particularly as they were not likely to get relief from dialysis with an opportunity of a kidney transplant.

Videos of the June conference were online and would be viewed and reviewed to get a better understanding of aHUS, its impact on aHUS patients and families. To get the orchestrated voice we needed adult and children (or their parents), male and females, those speaking for patients who died, that dialysis and /or plasma exchange, in remission and those few on eculizumab. We also needed family members. The search was on, articles were written for kidney patient organisation magazines, posting were made about aHUSUK on the EURORDIS social medium Rare Connect and the USA’s Foundation for children with atypical HUS website. Letters were written to those who had attended the Newcastle Conference but who had not come to Wimpole St. After

several weeks we had candidates for each of the categories we had decided upon, except male adult patients. We knew of a handful male by then, but all were reticent to participate.

It was evident that whilst Alexion knew about their drug and aHUS, it was weaker in its understanding of dialysis in its various forms and their co morbidities. Comparing eculizumab costs with a dialysis pack cost plus plasma exchange, although the latter by normal treatment standards were expensive, were nowhere near the cost of eculizumab. But the cost of treating the comorbidities, which although would not be experience by all each year would be experience by most at some time, some more than once. The search was on to provide such a list. Clearly our “patients’ voice “candidates would provide some of these, particularly those on dialysis for decades. But there was another source. Those from around the world who had told their stories on rare Connect or the children with aHUS websites provided considerable evidence and experience some the same some different. I began reading those websites and making notes of the additional treatments for comorbidities reported by people in the public domain. The aHUS social media is full of such data for research.

Eventually as months passed by the NHS got in touch with our “trustee for the patient voice” the role given to my daughter. AGNSS had decided that the patient groups submission should take the form of a piece of a written qualitative research. The NHS would provide qualified resource to do the leg work but the topics to be covered were left to aHUSUK to decide. Another month passed, and some consultants Toucan Associates were appointed. Working with the trustee for patient voice a range of key questions were chosen to be used in structured interviews with our “patient voice panel”. The interviews would be held either face to face or over the phone. The responses would be recorded and transcribed into written notes. Key themes from the responses would be identified and, in some case, illustrated with quotes from the interviewees.

Meanwhile a list of co morbidities was being drawn up to put in the research paper. Sadly, there was no time to research the costs of the comorbidity treatments.

Eventually a draft report was produced and at an all-day meeting of trustees it was read, amended and approved. It was mid-May 2012, the AGNSS meeting was to be held on 14 June.

aHUSUK had got its written evidence done on time for the AGNSS Committee to read before the meeting.

Had it achieved no more what aHUSUK had produced had fully justified the creation of the charity. It was an acclaimed and unique example of qualitative aHUS research. Had it not been held "in strictest confidence" for the whole time that eculizumab was to be evaluated it would have been an excellent standalone publication about aHUS. (A version of it including more interviews with Welsh aHUS patients can be read by clicking here).

However, there was more to be done to ensure the aHUS patient voice resonated the AGNSS saw and understood what is was like living with aHUS.

Chapter 7 Don't rain on our parade!

14 June 2012 London – AGNSS Meeting to Evaluate Eculizumab for aHUS.

This was it this what we had been preparing for. The aHUS Trustee for Patients Voice was the only representative for patients allowed to attend. The only one allowed to speak and was allotted 5 minutes to present to the Committee Members.

Alexion were there the bulk of the evidence submission was theirs. The case for clinical effectiveness and safety, the cost effectiveness and for how eculizumab was priced was for them to make.

As participants aHUSUK had been given rights to look at the written evidence presented to the Committee Members. There was over 700 pages of evidence including around 30 for the patient voice research paper aHUSUK had submitted. There were reports on the eculizumab trials, there estimates of patient numbers projected forward five years, there costs of eculizumab, there were costs of dialysis and plasma exchange, but no mention of costs related to damage done by dialysis. There were life expectancy estimates with or without eculizumab, there was research on the quality of life of dialysis patients. There was even a "cost per QALY".

The Cost per Quality Adjusted Life Year was a health service indicator of the cost effectiveness of new medicines and technologies compared with existing treatments. It involved estimates of costs of each, life expectancy in years depending on treatment used, and the quality of those year assessed on a scale between 0 and 1, where 1 was excellent health and 0 was no life. The difference in the quality of life for those on each treatment say 0.9 for one and 0.2 for another, 0.7 was multiplied by the difference in the number of life years to the quality adjusted life years which when divided into the difference in the costs of each treatment gave the "cost per QALY". There is a little

bit more jiggery pokery using accounting techniques to get to the figure.

Normally for medicines looked at elsewhere in the health service the QALY result would have to better £30,000 per QALY but AGNSS was not bound by that as it was designed for technologies for rare diseases. Just as well as based on the evidence given to Committee the Cost of QALY was many times that figure. In a way it just demonstrated that Eculizumab was an ultra-orphan drug. But was it reasonably priced?

aHUSUK's job was to show how debilitating and life-threatening aHUS was and that Eculizumab offered benefits "beyond price". We had our Patient Voice Report, but we also had five minutes to get the point across too. It was import that every second of the 5 minutes was used and no more. Every word had to count. Three trustees and their families met and spent 8 hours designing and developing the talk and it is supporting visuals. Run through after run through words were changed and times were cut until the optimum was reached. A five-minute talk emerged which said all that need to be said.

"One of the best presentations we have ever had" said the Chair of AGNSS after the Trustee for patient voice sat down after delivering the talk. A few questions followed and aHUSUK's job and from around the room there was a sense that a good case had been made. So much so that when the next speaker got up to speak even, he had to apologise for "raining on our parade". aHUS patients had felt the deluge of their illness so one drop more made little effect. His talk was about critiquing the evidence, he read his presentation out and sat down

We could do no more. The stakeholders including Alexion representatives and Prof Goodship, left the room. AGNSS went into a closed discussion during which they could call on stakeholders to return for further questions. We did not know what had been said nor decided; would not know because whatever they recommended

would need to be given to Minister of Health, who then was The Earl Howe, to decide on whether to accept their recommendation. We were told it was in a metaphorical “black box” until the Minster opened it and made his decision to accept it or not, then we would know what the fate of aHUS patients would be.

The meeting ended. We waited.

Chapter 8 The higher you build your barriers

Then came the announcement and the “No decision” conversation. (click **here** for that!)

To say aHUSUK trustees were incandescent would be an understatement. To keep us waiting for seven months on a decision that AGNSS had made and had approved eculizumab; and to say it was all to be done again because AGNSS was disappearing and to be replaced in April by NICE was deplorable. Appalling.

We were thwarted as there was no right of appeal. A great injustice had been foisted on to aHUS patients in England all because the NHS was to be re-organised and the Health Minister wanted a review on what “affordability” was and would use aHUS patients to find out. Another set of hurdles for an unfortunate cohort of people with a rare disease.

The Minister said that aHUS patients who needed Eculizumab could seek “Individual Funding Requests” (IFR). This was the process that had failed aHUS patients so far as it sought uniqueness within a rare aHUS cohort, so it could not be for all. It had created a postcode lottery and much discrimination even within families, and it was why a National Specialised Service was needed and had been applied for and which AGNSS had agreed to be given. Indeed, under the "new” NHS rules, if four patients got IFRs approved for a single therapy it would trigger an application for a National Specialised Service to be considered approved. That is precisely what going through AGNSS had been about. A suitable plot for a Gilbert & Sullivan comic opera or “Catch 22” type novel.

A bit of news that we had heard a few days before the announcement made us scratch our heads. The NHS had approved a national service for a specialised treatment for a rare disease. A rare cohort of those suffering from Cystic Fibrosis. We knew that the Cystic Fibrosis Trust

was raising awareness for a drug at the same time as us, I had even signed a petition that they had set up for the drug to be made available, such was our support for rare diseases by then. They were not in AGNSS programme at that time and so were behind us in the "queue"

Except once AGNSS had ended, and before they would need to go to NICE Cystic Fibrosis clinicians, the pharmaceutical company, the patient group and the NHS conspired to develop a bespoke evaluation and funding process while aHUS patients were waiting for the outcome of AGNSS. Within 3 months it delivered a Specialised Service to be delivered Nationally, but not a National Specialised Service which, of course, it could not be. (Good luck to CF patients it is an awful disease, as bad as aHUS, though perhaps not as immediately life threatening. It did seem that their drug did not appear to be as effective as eculizumab). aHUS patients could now die. It had been predicted that over 10 would die in the coming 12 months.

aHUSUK needed to act and would have to campaign, not for the drug to be approved, we did not need to campaign for that our Patient Voice did its job, now it was the injustice of a decision-making process for which we had no right of appeal. It was our appeal.

No right of appeal and the Minister making the decision refused to talk to us.

Oddly at around the same time we heard the results of an application we had made to a large kidney patient organisation, BKPA, it had turned down our request for financial support because it considered us to be a campaign group for patients, not a patient support group. We were doing both, we had not been political but advocating for aHUS patients, an extremely small group of people because of its rarity. Something this industrial size charity could not get its head around at that time.

BKPA would continue to keep large sums of money in its bank account for which reputedly it was getting criticism from the Charity

Commission about. We needed funds though as publicity for our cause could cost us. One of our members donated to the charity to be used for awareness projects. Along with that came excellent advice because this member had also had experience of campaigning for a specialised service for another rare disease **Pulmonary Hypertension** which affected her family as aHUS had too.

aHUS people were going to die but had no rights to life, and others surviving would be destroyed through injustice.

They had been treated wrong. So wrong

Something inside was getting so strong.

The higher they build their barriers the taller we became....

Chapter 9 Good will come, together?

Before continuing the U.K., front there had been an international development worth a mention which would transform aHUS advocacy not only in the UK but internationally, for all ahu's patients and organizations around the world.

aHUSUK had fulfilled an invitation from AIRG France to attend the national aHUS Patients Conference two days after the AGNSS meeting on 16 June 2012. Although not as comprehensive as was to be the case in future when reporting about conferences I attended, I wrote briefly on the Rare Connect website about the experience:

"*I would like to say thank you for my daughter and me. We too attended the 2nd Conference on aHUS in Paris.*

Professor Hubert Nivet, who made clear issues (about Complement) with his clever analogies and humour, Dr Veronique Fremeaux -Baachi whose enthusiasm and passion for understanding aHUS through research shone though, and Professor Chantal Loire's authoritative knowledge on matters aHUS is plainly evident. So were the other professors and doctors who talked about the treatment of children and adults, as well as the successes of transplants supported by eculizumab. All added to what is a positive and hopeful future for aHUS patients in France and indeed everywhere.

We shall therefore have the same questions, issues, concerns and stoicism in living with aHUS.

Thanks to Daniel (Renault) and Nicolas (Mullier) for organizing a worthwhile and successful conference at this impressive venue that is the Hopital European Georges Pompidou."

Little did we know it but the aHUS patient organisation representatives who attended the meeting from France, Belgium and Spain as well as the U.K. began to talk about collaborating between countries. A momentum then began building in the social media about

some form of international group, culminating in the first meeting of the aHUS alliance in Barcelona eight months later.

A couple of weeks after the AGNSS announcement the first meeting was held of what was intended to be the **Alliance SHUa European** a sub group of the fledgling organisation FEDERG. By then aHUS organisations from Italy and Russia had been added to its number.

The meeting took place in a hotel (America!) in Barcelona. After introducing each other, our organisations and what the status of aHUS was in our countries at that time a debate took place on what kind of activities could be done better together and whether a European organisation should be formed to do them. Those attending said that such an organisation, a loose affiliation (i.e. not a formal legal entity) should be formed (later amended), and it should not be confined to Europe and that it should be called the **aHUS alliance**. The group was to be associated with Rare Connect, whose representative also attended the meeting (a EURORDIS project) and whose on line platform would be used for communication as no alliance website was intended to be constructed. It was on Rare Connect that the formation of the aHUS alliance was announced on 28 February 2013 - Rare Disease Day.

But could good come from being together?

Chapter 10 What do we need? When do we need it?

Back to the U.K. and OK putting the rhetoric aside for a while, we were facing another hurdle but just what could we do about it?

We were by then a rare disease organisation with the families of about 15 or so aHUS patients as members. We knew of another 15 or so aHUS patients at least; but they were not prepared to join with us. There could have been the families of another 150 aHUS patients, but they probably did not know what was happening for them and about them.

We had to decide what we wanted, and then have plans to act which would not overwhelm a small, and it must be remembered, still ill group of people, with little or no resources.

We could not be political; aHUS people are from all sides of the political spectrum. It would too easy to go to a newspaper which supports an opposition political party to have a go at the political party in power. That be would wrong.

On the day of the Government's announcement about the AGNSS outcome, the aHUSUK Secretary was in Parliament attending and talking to a meeting called by the Opposition Health Minister about Rare Disease treatment access. This politician had been banging on for months in debates about how the implementation of Government reforms of the NHS would present high risks to patients. On that day the aHUSUK Secretary was able to give him a newsworthy example of how Government changes had put a small group of patients at grave risk. He did nothing.

Neither did the Health Minister who made the unjust decision and who was not even prepared to meet and discuss his decision with us.

A media campaign was out of the question. We sought advice and were told it would cost us over £100,000 and we would have to do a lot of the work. We could not afford that.

We would have to find a way that reporters and journalists would come to us for free but remembering that the Government and its agencies had public relations budgets of £ millions. It would be an unfair competition. Our strength was we were the victims in more ways than could be imagined.

But what would be our message about what we wanted.

We wanted AGNSS recommendation implemented

We wanted it done quickly

We wanted aHUS dialysis patients in scope

We wanted to influence NICE from the outset.

With the latter we were conceding then that we would be the "guinea pigs" for NICE's new process but in return for that, we wanted aHUS patients, there and then, to be treated equitably while the review took place.

We also wanted equity built into what NICE did.

SO, **JUSTICE** and **EQUITY.**

So, our aim was "to get eculizumab right then for aHUS patients who needed it for as long as they needed it"

So then

"What do we need.....?"

"**ECULIZUMAB"**

"When do we need it? "

"NOW"

Repeat!

Chapter 11 The finest hour of the few.

So, we now had a message and had a target audience in mind and some plans for how it would be delivered.

But what started as four hours a month task at the start had rapidly passed four hours a week and was now four hours a day for most aHUSUK trustees and would now move to 2 to 3 times that for some. We were doing what Public Relations professionals would do but in our case for no pay but just because it mattered very much. (Probably a key test for patient advocacy if it does not matter that much, do not do it).

Members of Parliament (MPs) were our first key audience. Earlier aHUS patients and their families had been asked to write to them to tell them about aHUS and the AGNSS evaluation of eculizumab. We were advised to do that because MPs would have to write to the Health Minister who would have to reply. That correspondence would all go into a "file" at the Department of Health. The replies from MPs fell into the pattern "The treatment is being considered by AGNSS, so they would have to see the outcome before taking further action".

AGNSS recommendation was now known and aHUS patients had been treated unfairly so we asked them to take up the case once more. They did but now there were more than twice the number of letters sent and the Health Minister had to justify why the health reforms were punishing this small group. The file had grown considerably, and this was just for a very rare disease patient cohort.

There was another way to make MPs aware and that was through an 'Early Day Motion" which if sufficiently supported could permit the matter to be discussed in Parliament but if not would raise some awareness. Sadly, this is a much-discredited element of parliamentary democracy because it was in competition with nonsense motions about "support for football teams which had been promoted or won a cup competition"

There was one other way to get it into Parliament and one which would be a major challenge and a very high mountain to climb. The petition.

There were two types of petition - written and online

The online petition or e- petition was a formal process run by parliament itself which offered a formal response from the relevant Health Minister if at least 10, 000 people signed it. It would also be debated in Parliament if 100,000 people supported it. We had supported an e-petition previously submitted by an organisation of aHUS clinicians to raise awareness and which was expected to raise a few hundred supporters. aHUSUK got involved and raised over 2500 signatures. Not enough but we were told that it was someone's job at the Department of Health to monitor emerging issues and we had got aHUS on to the first page of Health issues and into view.

This time it would be aHUSUK that would be the petitioners and we would need to get many more people involved and get many more to support us. We wanted visibility but moreover we wanted a response from the Health Minister.

The written petition was the traditional democratic process. It could be delivered directly to the Prime Minister to get the Health Minister to act or could be handed over to the Speaker in Parliament by an MP or MPs to go to the Health Minister to respond. We applied for it to be done both ways.

All very well but we had to get signatures. Firstly, we created a call to action portal on our website. Anyone wishing to support the e-petition could be taken directly through to the "signing page" by clicking on the portal button. But we also needed to get people to come to the site and this was going to take more than newsletters to our members. We also created Facebook and Twitter Accounts.

The social media is a very powerful tool when it comes to gaining on line support. Posts and tweets to primary followers need to be shared

and retweeted by them to their followers and so on to other followers if the petition was getting the outreach to get petition signed. And it happened on some posts a reach of 20,000 or more was achieved, not all led to signatures but if 5% or 10% did it would boost numbers greatly. It was also a good thing if someone with a high profile with lots of followers was to support you. The lead singer of Dr Hook (songs: “Sylvia’s Mother” and “If you’re in love with a beautiful woman") Dennis Locorriere gave his support and asked his fans to sign our e-petition.

We began the e petition on 26 February and by Rare Disease Day 48 hours later we had already got 1000 signatures. We set ourselves a target to get 10000 signatures by St George’s Day, 24 April and “By George we got it”.

Our petition was in the top three health topics and matching topics affecting 100, 000s or more people.

The written petition demanded a different approach. It could include those not on line and was easier for all signatories to do. Families were galvanised asked all and sundry to sign the petition, neighbours, parents in school yards, window cleaners and so on. Some grandparents also stood in town squares and asked passers-by and others stood out football grounds and got 1000s of support signatures.

By 25 March we were booked to present the first tranche of the petition containing 15000 signatures to 10 Downing Street. 6 members of aHUSUK were allowed into Downing St to hand it over. It was filmed and featured on national and regional TV.

Some images of the presentation can be seen **here** *and* **here**

The second tranche was to be handed over in the House of Commons and split between two MPs who had been asked and had agreed to

support us. So, another 20000 to 30000 signatures petition were duly handed over some six weeks after the Downing Street handover.

In addition to this some aHUSUK members had appeared on national and local radio and TV, as well as in national and local newspapers. A small number of aHUSUK members had created considerable noise, all of which was being noted at the Department of Health. It was now May 2013.

It had mattered to aHUS patients and so the few had done it for each other, even for the benefit of those aHUS patients yet to come, even for those who had chosen not to join in the battle.

The aHUS few's finest hour.

Chapter 12 If you want our help, help patients

By May 2013, after nearly three months of campaigning by the "few" and getting the issue to the attention of the Health Minister and Department of Health, two notable events happened.

In April NICE had taken on responsibility for evaluating eculizumab for aHUS but was not ready to do so and it expected to begin its work on eculizumab in December.

The e petition response from the Department of Health confirmed this, but also said that in the meantime another NHS group would look at the service to be given in interim period.

So, the NHS had shifted its position and was now prepared for an interim policy to be implemented ahead of NICE. Starting with all new onsets. A newly created Clinical Priorities Advisory Group decided at its first meeting that new onset aHUS patients were a priority for treatment. The first sign of a change of mind but we also wanted to bring aHUS dialysis patients in scope for a transplant. NHS now had to do it via this new group which had been set up in the NHS reforms. Whilst yet another hurdle for aHUS patients to get over there would be no more discriminatory individual funding requests in a post code lottery.

By July 2013 CPAG held its second meeting which aHUSUK Trustee for Patient Voice, along with Alexion and Prof. Goodship were invited to attend and present to the Group (our research document was the basis of the patient's voice, it had been added to and improved upon since the AGNSS meeting, so we were confident it would do the job.)

Immediately after the meeting we were told that an interim aHUS Service had been approved for all aHUS patients, and it would be included in the NHS Specialised Services list for 2013/14. The service would be interim one pending the review of eculizumab by NICE.

The CPAG meeting was the day after the first formal meeting by NICE to define the scope of the evaluation of eculizumab for aHUS. So, with that we were back to the stage we reached with AGNSS in October 2011 but with some progress made for existing patients.

We can never be sure what went on behind the scenes, but this shift was announced following the aHUSUK campaign and the noise created by tens of thousands of people who felt we had been poorly treated. Even the Health Minister invited aHUSUK to visit him finally (Sylwia an aHUSUK member had telephoned a radio programme with the Deputy Prime Minister as a guest and who agreed to arrange a meeting with the Health Minister) and welcomed our intention to help NICE develop its new Highly Specialised Technology evaluation process providing existing aHUS patients were treated.

So, we would be doing it in the knowledge that aHUS patients known about there and then would have access to eculizumab even those who were trialists and those who needed a transplant.

If NICE turned down eculizumab for aHUS at the end of its review future aHUS patients, including those on dialysis who could not be transplants in that time, would not be treated.

Our job now was to help NICE make the right decision that eculizumab should be given when needed for as long as is needed.

Chapter 13 Affordable means able to afford

The evaluation of eculizumab for aHUS was now needing to be carried out by NICE, even though it had already been evaluated and recommended by another group. This was called for by the Health Minister because he wanted a view on whether eculizumab was affordable by the NHS for the treatment of a small number of rare disease patients.

Eculizumab had already been deemed an approved highly specialised technology for the treatment for patients affected by Paroxysmal Nocturnal Haemoglobinuria, or PNH; so, the question now really was "was it affordable for aHUS too?". What had happened for PNH patients was irrelevant. Neither could support to our cause from those PNH patients be expected.

However, it could be said that what was going to happen to us was going to have a bearing on those rare disease patients who were going to follow us in the NICE process. There was a great responsibility on our shoulders.

Affordability. Eculizumab came at a price and NHS England had resources from taxation etc. of over £100 billion, £2 billion a week and rising some might put it. The cost for a small number of rare disease patients was well within its means. So that could not be the test of what affordable means.

The finances and economics of health are both complex and confusing subjects, with inconsistencies throughout, so to get a simple answer for the Health Minister was not going to be straight forward. That was aHUSUK's worry. An unanswerable question being posed for debate when patients were suffering.

It is at this point that awareness grows that there is no human right to life when it comes to decision processes about providing treatment to patients. This does not mean that those making the decisions do not care about people, it just means that they are protected from any

action against their decision on the grounds of abusing human rights to life, because it is ruled not an abuse. Not many people know that.

Another issue which emerges is the lack of clear thinking on financial and economic terms used. In the time aHUSUK had been involved, and particularly in communications supporting the Minister's decision, we had heard about need for cost effectiveness, reasonable price, wise use of NHS resources, a cash strapped NHS, value for money, value-based pricing. All of which mean different things and are mostly subjective in nature with rarely an acceptable established methodology to arrive at an indisputable conclusion. Cost effectiveness in health economics "science" means lower incremental cost per QALY. QALY has been mentioned before and is a difficult concept to understand. Those defending using cost per QALY as a methodology were apt to defend it from critics by saying "that if you cannot find three flaws in the QALY process you do not understand it ".

Hardly a ringing endorsement but the flaws apply equally to all and it is the comparative result between treatments which is important.

But cost effectiveness as determined by QALY assessment, although egalitarian, does not necessarily mean affordable. Neither would it be equitable, it would only apply to a small fraction of total NHS spend and would be institutionally discriminatory against those needing ultra-orphan drugs. In QALY assessments for aHUS patients their quality of life after treating would need to be 1 on scale of 0 to 1, having been 0.1; or with eculizumab they would have to live in such perfect health for 300 years or more. Not going to happen.

aHUSUK would focus on affordability being what the "cost" of treating the aHUS patient cohort would be. That would be determined by the number of aHUS patients there were and what the average cost of eculizumab doses needed would be. Quantity x Doses Price. The drug budget.

Following that our focus was on the cost of other uses of NHS resources using the principle that “when escaping from a lion you do not have to run fast, but just need to run faster than others running away”. That is how NICE would be looking at it effectively, in a cash strapped NHS are there other treatments that are less beneficial that could be given up affording the treatment of aHUS patients? The **opportunity cost** as the experts call it I.e. the cost of the foregone alternative.

Thirdly aHUSUK would look deeper into the price of eculizumab and what elements make up its price because for all the academic nature of such health evaluations, the main concern remained “was Alexion's price for eculizumab a “rip off” of ultimately the tax payers who fund the NHS?”. Making profit was acceptable for the sustained availability of eculizumab, but as the market sales grew and costs of sales reduced, and overhead costs fixed, where was that sales growth dividend going?

aHUSUK had come a long way since it was formed with barely anything but a personal knowledge of a family member’s encounter with aHUS. The trustees were now learning about concepts and methodologies used by experts, but without the training and experience of these experts. Armed with common sense and a growing confidence in what to challenge and how to do so, we still needed to punch way above our weight, but do it now in a high-profile formal evaluation process which was being developed in front of our eyes.

Affordable clearly means a lot more than simply an ability to afford.

Chapter 14 One step at a time

NICE was not ready to begin its work on eculizumab when it took over responsibility for the job as part of the NHS reorganisation. It had done no preliminary preparation because the organisation itself was going through change and the outgoing Chair of NICE, who had known about taking on this responsibility for at least 7 months, decided to leave the management of its implementation to his replacement. The replacement would take over from 1 April 2013. No joking.

However, there were several people who had been given the job of communicating the change decision. A meeting had been called with potential stakeholders to explain the implications. aHUSUK had not been invited to attend. This did not auger well as a start.

However, having complained about NICE's snub to aHUS patients we were invited to meet them in their London office.

Understandably we told them that we did not believe we should be going through this again having gone through it with AGNSS, we were not happy to do so. We said that we did not think they would come to a different conclusion. We said to remove any doubt it needed to build equity into its process and properly address the affordability question. We insisted that getting the NHS to let it be known how many aHUS patients there were and who needed treatment and for how long. We could not believe there was as many patients as estimated which had raised doubts about affordability.

By then we had found out the work on treatment adjustment taking place in Milan clinic, having heard about it from the alliance affiliate from Italy but this was not what we meant. Just the mix of patients on different doses levels for weight would have a bearing on the actual average cost per patient. Similarly, we did not believe the projected number of patients within five years needing eculizumab for life was

right. Neither was the estimate of existing numbers of patients. If that basic budget forecast was flawed how could affordability be assessed!

We were told NICE would try to devise a methodology for comparing resources on an opportunity cost basis as part of its decision making. However, there was a feeling that this would not be robust. We did not believe that the relative societal costs would be adequately reflected. aHUSUK had contacted a Professor Jennifer Roberts of the London School of Hygiene and Tropical Diseases. Prof Roberts along with Professor Jennifer Busby of the USA were eminent authorities on the true cost to society of E. coli outbreaks, of which typical HUS and its implications had been researched. The costs off the alternative to eculizumab they found were higher than those used in the AGNSS process, including the impact on society. The morbidity and outcome for aHUS patient not transplantable would be higher still. We thought that NICE should look at that too.

Finally, we asserted that this whole process would be improved if the NICE committee had a qualified accountant on board to give a professional opinion on the profitability of the price of the drug because that was a key determinant in the decision. Health economics was not enough.

So, before we got into the process, we had made clear that unless changes were made a similar non-conclusive outcome would be likely due to incomplete evidence.

Another example of aHUSUK's advocacy going beyond just giving the patient voice about the disease. However, for the process we would initially be giving evidence about the illness again. We would have to bide our time on the finance and economics.

We will get there just one step at a time.

Chapter 15 NICE Process begins it will soon be Christmas

NICE manages each evaluation as a project. Each evaluation is assigned a Project Manager. A Project Management Methodology is used to plan and control the operation in a logical manner.

The evaluation is broken down into stages and each stage results in a "product", such as a document which defines the outcome and decisions made.

Each stage has a gathering evidence step, evaluating and decision step and documenting and communicating the decision step and then a consultation or quality assurance review step (or steps as the latter can be repeated) before the stage is complete and the project moves on a stage.

In April 2013 we heard that NICE would not get to the evaluating and decision step until December 2013, which would be over two years since aHUSUK had been created, none of the trustee advocates had expected that.

Although we were also preoccupied with the Clinical Priorities Advisory Group, we began the NICE process by responding to a request to comment on the scope of the "eculizumab" project. We answered the questions posed and then attended a meeting on 13 July at NICE's office. We were shocked by the numbers attending the meeting; NICE tended to make its consultations public affairs. Anyway, it seemed that aHUSUK had responded with the most detail and the conversation mostly addressed our views.

The initial stage of the NICE evaluation began with this scoping stage -where it establishes and defines what they are going to examine and how they will do it.

They decided: -

- they were reviewing eculizumab;

- to be used for treating atypical Haemolytic Uraemic Syndrome;
- and compare it with other treatments including plasma exchange and dialysis and combined liver/kidney transplants;
- they will gather clinical and economic evidence from the manufacturer;
- they will gather patient impact data from the patient organisations;
- the evidence will be gathered in a format they have devised for the Evaluation Group led by Prof. Jackson;
- evidence will be gathered over the next eight to eleven weeks;
- NICE will only meet with evidence suppliers if they need to test understanding or seek more data;
- Otherwise the next meeting will be on 11 December 2013 when the NICE HST Committee meets to decide.

So aHUSUK now had to complete its Patient Voice Submission in less than two months, which in effect meant improving the original AGNSS submission by adding the Welsh Patients testimonies, the data gathered from a Survey Monkey and for other meetings, including CPAG. We hoped members, including those from Scotland, would continue to feed into the process and make it a very compelling document.

The meeting was a very positive experience because the NICE staff were keen to develop an ultra-orphan evaluation methodology, and so many clinical experts attended who were very supportive of eculizumab for their patients.

Looking back despite how much we had developed as a patient group, our understanding of aHUS within the context of all thrombotic microangiopathies was just beginning. That knowledge would have benefited us more in understanding potential patient numbers for inclusion in the scope for treatment. We would know now that it was only those TMAs that were “Complement mediated" which should be in scope, not other secondary causes of aHUS,

thereby reducing the costs to be afforded. Although there are overlaps between categories that could apply.

With the scope defined, the next step would be supplying evidence of what it is like for those affected by aHUS, that evidence was called for in late July and had to completed by 9th September. Less than 2 months. Fortunately, aHUSUK already had its evidence. Indeed, we had improved it with interviews of 4 Welsh patients and a carer. Doing it ourselves it revealed how hard a job it was to interview and record participants. Then transcribe the interview word for word before analysing the thread of the discussion to determine unique or confirming comments to use, and specific "sound bites" to make the point in a memorable way.

Except NICE had decided to use an on-line questionnaire for patient organisations, but when we tried to copy and paste the content of our evidence research into the relevant questions, the system crashed. We were providing "too much" evidence but to precis it would ruin and diminish the work we had done. We were going through an unprecedented third evaluation process not of our making. We complained to NICE and it was agreed that we would map and cross reference relevant questions in their form to the sections of our research document, and we would append our full report to read. That plus some administrative details and closing comments was our submission and it was provided on time.

The next step in the evaluation process would be the holding of a meeting of the Evaluation Committee. We would be expected to attend. Indeed, two representatives were allowed, and it was decided that I and another trustee, who had been an eculizumab trialist, would provide any additional answers for the Committee at this meeting.

NICE, unlike AGNSS, did not want a presentation, so we had no control over what we would expect to say. So, we made a list of possible points we wanted to get across when a relevant question

was raised. We would answer the question prepared for but not necessarily the question asked! All the contact with politicians was now rubbing off on us.

Eventually we were advised that the Committee would hold its meeting in public, unlike the AGNSS meeting at which only stakeholders attended along with the Committee.

It was scheduled for 11th December 2013 and the result would not be known until 2014 but with an intention to complete the project by July 2014. A year on from the scoping meeting and nearly three years since aHUSUK was created.

In that time an additional 75 English patients were likely to have onset with aHUS most of whom would not have known about the illness they had. At least now they had the safety net of the interim service.

Another Christmas was to pass before we would see the outcome of what we had come together to achieve.

It was not be a foregone conclusion and our anxiety about having to do this again was evident in this extract from a press release by the charity shows.

aHUSUK GOES TO NICE: Press Release

Ahead of its appearance at NICE when eculizumab will be evaluated again, aHUSUK has released the following statement.

PRESS RELEASE FROM aHUSUK (www.ahusuk.org)

Anxious Patient Group calls on NICE to approve only drug treatment for ultra -rare disease

Fight for treatment over three years – NICE Committee in the spotlight as it evaluates first ultra-orphan drug

On 11th December the National Institute for Health and Care Excellence's (NICE) First Appraisal meeting is taking place to judge whether eculizumab should be recommended in England as a treatment for the ultra-rare disease atypical Haemolytic Uraemic Syndrome (aHUS). National commissioning of this drug for the treatment of aHUS was recommended in June 2012 by the Advisory Group for National Specialised Services (AGNSS) which stated, "It is clear that eculizumab is an effective treatment for aHUS and gives a much better quality of life than the alternative treatments". Patients' elation turned to horror when, following this recommendation Health Minister, Earl Howe, unilaterally decided that the drug should not be made available to sufferers, but must undergo a further evaluation by NICE, the first time NICE has ever had to approve an ultra- orphan drug for a rare disease. Eculizumab has already been approved for treatment of aHUS in forty other countries and is even commissioned nationally for another rare disease in England.

Sufferers of aHUS have been living in a state of limbo. Some have been able to access the drug, through interim funding measures and clinical trials, and are waiting anxiously to hear if they will be able to continue to take the drug and lead a normal life, or whether they will have to revert to previous treatments such as plasma exchange or much worse, be condemned to renal dialysis for the rest of their much- shortened lives. The fight to get any access to this life changing treatment has been hard – in March and May of this year we delivered petitions to Downing Street and the House of Commons calling for everyone to be able to have access to this miracle drug.

"Eculizumab is the only treatment for aHUS. Everyone, including ministers, NICE, AGNSS, CPAG and clinicians in the field, agrees that it is clinically effective. Dialysis and plasma exchange are ways to

manage the disease but with this management strategy aHUS sufferers cannot work, cannot travel far from hospital and must endure horrendous treatment side effects. Eculizumab allows sufferers to live a normal life, to work and contribute to the economy. We urge NICE to think differently when it comes to payment for and commissioning of treatments for very rare diseases that have devastating effects on a few sufferers. We trust that its Evaluation Committee will show it can make well-rounded decisions for rare diseases, like its highly regarded predecessor, AGNSS, and will not condemn all aHUS patients to horrific and foreshortened lives,". Ian Mackersie, Secretary of aHUSUK Patient Group.

"Our lack of confidence in the process of approval for this drug, given it has already been approved by two previous evaluations [AGNNS and CPAG], has meant we have had to fight publicly to try to ensure NICE does the right thing. The treatment is life transforming. aHUS patients previously had no light at the end of the tunnel, now they do. Surely, they too deserve the right to get the very best care available today. NICE can take that bright horizon away from us and we cannot let that happen. This is a heavy burden for aHUS sufferers and their families to shoulder in addition to coping with living with this terrible disease". Emma Woodward, Trustee, aHUSUK Patient Group.

Chapter 16 And keep those plates spinning while you are at it

Our NICE evidence was submitted on 9 September 2013. The day after that it was the second anniversary of the forming of aHUSUK. That day we heard that the interim aHUS service recommended by CPAG had been ratified by the NHS Board. It would be three months until the next NICE meeting.

Time for a rest. Not so.

Two years after its creation aHUSUK was very active in the communities relevant to aHUS - Renal- Rare/Genetic -Complement- Specialised Health Services. The reports on aHUSUK's website in that period reflect that.

-The charity was invited by the Bio Industries Association or BIA for a "breakfast meeting" in the House of Commons with politicians, pharmaceutical industry and health organisation representatives. We were, uniquely, able to comment on an experience of going through two evaluation processes for a treatment for our illness AGNSS and NICE. It was interesting to hear the industry's side of matters and their commitment to and investment in research; and one statistic was very surprising. Of the €70 billion invested in research into developing medicines for rare diseases, €60 billion is invested by the US government and Pharmaceutical Companies in almost equal measures and a creditable €5 billion by academia/patient-based

charities. Leaving just €5 billion spend by the governments and others in the rest of the world. If true rare disease patients depend a lot on the USA. Makes you think.

-We attended the first public meeting of a new major project for cancer and rare diseases. ***The 100,000 Genomes Project.*** Its aim was to undertake full genome testing of 100,000 patients in England. This was being done to find possible genetic causes of their diseases. aHUS was just one such diseases that had a genetic cause. However not all genetic reasons had been discovered. Nearly 40% of those tested were found to have no known genetic mutation. The meeting was held in the Great Hall of St Bart's Hospital London. Its walls were covered with 18th century murals painted by William Hogarth, another historic and impressive building visited as a patient advocate. aHUSUK was fully supportive of this project even though aHUS patients would be a very small number of potential participants.

- aHUSUK had been asked to join the Rare Disease Group for aHUS. This was an initiative was led by the UK renal professional body "The Renal Association "and funded by the major renal charities like Kidney Research UK. The group's task was to set guidelines for the diagnosis and treatment of aHUS. It also provided encouragement for research into the disease. It was chaired by Professor Tim Goodship.

- We also attended the annual meeting of Complement UK, an organisation set up to develop knowledge and understanding of the Complement system and its impact on diseases such as aHUS. That meeting was an eye opener in so many ways not just from the presentation on aHUS but also how different mutations in different components of Complement led to it having too little or too much activity result in a spectrum of diseases. Complement plays a part on its own or in conjunction with other parts of the immune system in diseases such Alzheimer's, Multiple Sclerosis, Parkinson's, Antiphospholipid Syndrome, Age Macular Degeneration, as well as

renal diseases like Lupus, MPGN and aHUS. ***Complementology*** could be an important specialism in the future!

- Soon after aHUSUK attended a meeting about all Renal Rare Disease Groups in Peterborough to develop a cross group understanding and support. Inspired by one patient representative that meeting led to an aHUSUK research fund raising project. But that was one for the future.

- aHUSUK thoughts were also turning to the next Rare Disease Day, to a project to create an artwork to be revealed on that day, the "Raise Your Hand" was seeking the names of 2000 patients to be a “named hand " and aHUSUK was encouraging as many aHUS patients and carers as possible to join in and show support.

- aHUSUK had given evidence to the Scottish Government about how health technologies for cancers and rare diseases were evaluated. The work of the Scottish Medicines Consortium, a sort of NICE for Scotland, had been studied by a Government Committee which had been set up following petitioning by the Rare Disease Community. Most drugs for rare diseases had been turned down by SMC unlike those for common diseases. That Committee had submitted its report. The Scottish Government was consulting stakeholders on its proposal for change. aHUSUK provided its views.

- As was the case in England and Scotland NHS Wales was also re-evaluating its processes for highly specialised technologies undertaken by the Welsh Strategic Health. aHUSUK were invited to attend a focus group meeting to provide feedback to the task group which would be reporting its recommendations to the Welsh Government. It did begin to seem more than coincidence that all UK health authorities (Northern Ireland would follow what was happening to NICE) were suspending, reviewing and changing their process just as Eculizumab for aHUS had entered or were about to enter evaluation.

-Genetic Alliance UK were working with the NHS and NICE to design a "Patient's Charter for the appraisal of rare disease treatments" As aHUSUK had experiences of AGNSS and uniquely NICE too we could contribute a lot to the discussion, although with great care as we were during the NICE process.

-three trustees attended the Annual General meeting and Conference of the National Kidney Federation and stood a table in the exhibition area to raise awareness about aHUS and its kidney patients.

-Of course, the charity itself had to be administered and the third general meeting was held in Solihull in the centre of England to make travel more equidistant for those in all regions. Apart from the administrative part of the day, including the "Treasurers Report" a role I had been volunteered for, part of the day was given over to a conference about aHUS. Prof Goodship continued to give his support with updates about developments in aHUS. The conference was also addressed by Phyllis Talbot a director of the USA's not for profit patient group, ***The Foundation for Children with atypical HUS***. She did it while driving with her family from her home in Atlanta to Baltimore for Thanksgiving and it was via Skype, projected on to a large screen. A technical feat only spoiled by a hitch when the connection was lost at the end and before she could see the standing ovation she received. aHUS was a small world and aHUSUK's outreach to other countries patient groups was growing.

Yep there was much to do still, and this period illustrates how running a charity made more and more demands on its volunteers and their time

Keeping plates spinning just while we were at it.

It being the main aHUSUK objective to get eculizumab approved free for all patients when they needed it for as long as they needed it.

Why would anyone be reluctant to do all that?

Three months passed quickly and soon it would be the 11th December 2013

CHAPTER 17 11th December 2013 (Part 1)

It was a cold, crisp and frosty morning in Manchester on 11th of December 2013. Above the sky was vivid blue when it could be glimpsed through the fog that shrouded much of the UK that day. Road conditions were poor as I set off to the city.

Once inside the NICE office in the centre of Manchester, we were taken to the 20th floor of the Tower and the view confirmed that, above the fog, the day was bright and clear into the distance; but all the well-known Manchester landmarks were invisible.

The Evaluation Committee meeting began with the Chair explaining how the meeting would run. After introductions and declarations of conflict of interests the witnesses were addressed in turn.
Giving evidence, apart from ourselves, was Prof. Tim Goodship and a Dr Rodney Gilbert from Southampton Hospital, the NHS Specialised Services leaders (including Dr Edmund Jessop 2019 Winner of EURORDIS' "Policy Maker Award"), and a team from Alexion. The academic guys from Sheffield University, who were expert in health economic evidence critique, were also there. The Evaluating Committee was made up of clinical experts from a range of medical roles, some lay members, and were supported by officials from NICE itself, some of whom we had already met.

No patient presentation had to be made, instead one of the Evaluation Committee's lay members summarised the case from our patient submission. His conclusion was the evidence was “rich and robust” and that “it made a compelling case for a call on NHS resources”.

WOW! The only issue now was that I and the other patient representative said nothing that would detract from that view! The only criticism of our report was that there not enough stories about patients who had received eculizumab. That was true, but few had

accessed it so far and only some of those who were trialists were known to us at the time.

It had been difficult to find aHUS patients, as we had told NICE at the outset, and eculizumab had not been approved so by definition such patients were few and far between. However, my aHUSUK patient expert colleague was a recipient of eculizumab but was not included in the report as it had been completed before she joined us. She was able to tell the Committee how ill she had been with loss of kidney function and needing dialysis after plasma exchange became less and less effective. She had been included in the eculizumab trial and was given doses of the drug. Soon her aHUS came under control and she recovered some kidney function. She came off dialysis and began to feel better. With better health she returned to work and got married. She was also starting a family. That is what eculizumab can do.

When asked for any concluding comments I remembered what my daughter had said at the first AGNSS meeting. Eculizumab for those on dialysis meant FREEDOM. Freedom from living a life around a dialysis machine, Freedom to eat and drink as we all do, Freedom to work and have a full life again. It goes without saying that those newly onseting would no longer need to know what that aHUS life would be like.

Unexpectedly the expert from Sheffield University in his critique mentioned an article on the aHUSUK website about a visit to Milan to find out more about the pioneering work of Dr Gianluigi Ardissino in adjusting and tapering the doses of eculizumab in his patients, and with some withdrawing from treatment once stable. This of course meant, unlike the “licensed full dose for life” on which the Committee had to consider the drug, that the average cost per patient would be much less. We could not have brought that up, it was not part of our evidence, but now it was part of the discussion and some doubt about the true treatment cost had crept in. Eculizumab when needed for as long as needed. It should not be wasted at that price.

The morning session went very quickly and there was a break for lunch. The meeting was going very well. In part of the afternoon session Alexion was asked to talk to the Committee without anyone else present; such was the commercially sensitive nature of the talk about its price for eculizumab.

It was a relief when the meeting ended and “witnesses were released”. I do not know if it had been the coldness of the day or the dryness of the air-conditioning, but by the beginning of the afternoon my voice was disappearing and became croaky! Maybe it was nature's way of saying “shut up and say no more, the patients' voice had already done its job”.

The Committee would spend the rest of meeting making its decision in private. Our main concern was about what Alexion had said during its closed session, it could be very detrimental.

We had been told that the next step would be the release of the Evaluation Decision document (the “product” of this stage). It was likely to be published sometime in late January 2014 (after our third Christmas as a charity).

Personally, none of that seemed to matter to me for now because during the lunch session a message had got to me (I was not one for mobile phones!). It was from my wife. The hospital had called. There could be a kidney for my daughter.

There was no rush!

CHAPTER 18 11th December 2013 (part 2)

It may seem odd that on the very same day that NICE was making its decision on whether eculizumab should be made available for aHUS patients throughout England that my daughter could be about to receive it to support a kidney transplant.

Some might say that this was because of the CPAG decision to extend scope of eculizumab to dialysis patients. That was a possibility.

Except my daughter had been called as a potential recipient twice before. Those calls came before the CPAG decision. On those occasions the kidneys were thought to be too marginal for her and they might be have been donated to the "reserve patient" . Reserves are always called up and most are disappointed and stand down.

So why had this happened at all?

Our knowledge about eculizumab's existence went back to before 2004. We were not told its name but in passing in the hospital corridor her transplant surgeon from her first transplant mentioned to my daughter that something was coming which could be of help. In 2004 work began for a transplant listing work up but was stopped when a doctor said that he would seek Prof. Tim Goodship's advice. Nothing more was heard, but at every clinic she asked how the listing was going, only to be told that her notes said that this doctor was still looking into it.

My daughter had not been on the transplant list before her first transplant, that same doctor from the near derelict hospital she was treated had failed to do so. So, her first transplant was with a kidney donated by her mother. That was on the Thanksgiving Day 1999. By Millennium Eve the decision was made to remove the failed graft. aHUS recurrence was the cause, but it was clear the clinicians treating her had no idea until we told them that it was a possibility and that she should be given plasma exchange. We were ignored and

dismissed. But we continued and eventually she was given fresh frozen plasma, and not PEX, to treat the TMA. Although they now, looking back very recklessly, zapped her whole immune system for rejection, putting her at risk of infection, it was too late. It then emerged that the promised management of her transplant between the derelict hospital and the one where the transplant took place had failed because of politics between two organisations which were going through a managerial change.

Had she been on the transplant list the fact that the graft failed within six months, it did not last 6 days, would have meant she would have retained her waiting time credit, which would be important in a future allocation decision, all other things being equal.

Even if she had been put on the transplant list in 2004, she would have accrued 7 years waiting time. When we asked Prof Goodship at the Wimpole Street meeting in 2011 what would happen to aHUS patients who had not been on the transplant list. He said they would go to the bottom of the list. So even if a decision was made to provide eculizumab my daughter could be looking at a further five year wait. That seemed unjust as those aHUS dialysis patients who had been listed but suspended and not transplanted (which was protocol) could have accrued enough time to be top of the list when their temporary suspension was lifted. What should be a fair and just system of allocation was, in practice, flawed.

So, when we left that first aHUSUK meeting in London we were determined to address that injustice. For that we had to switch to private patient engagement advocacy.

We began by writing to the hospital quoting the six-month rule. We were told with some certainty that would only apply if someone had been on the kidney donor list. Correspondence continued until we asked whether it was accidental (negligence) or deliberate (wilful) whether she had not been treated fairly by that Doctor. The correspondence continued and escalated through 2012 so by the end

we were having to write through the Chief Executive of the hospital such was the nature of the "complaint" it had become.

The hospital was saying that it was my daughter's fault she had not been listed because someone had written in her notes that she had said that "she had not wished to go **BACK ON** the list". It was that "note" on which the hospital was defending its position. But when we pointed out she could not have said that " because she had never been **ON** the list" the Hospital relented and agreed to approach the donor list authorities to put right her waiting time. Private patient advocacy can work but it is not easy. It takes an enormous amount of time to do (and we were also active in public advocacy too). There can be much resistance to your view, however right you may be. It also emerged that the doctor who everyone thought had been reviewing the advice for now eight years had not been at all but had neglected to tell anyone. All this could have been sorted out years before if communication had been up to professional standard. The precedent having been set would change the policy and benefit all aHUS similarly affected.

The other factor that may have had a bearing on the call up before eculizumab was approved for dialysis patients, was that during the correspondence with the hospital one doctor said that we should apply for an Individual Funding Request, IFR, for eculizumab. No IFR had been approved for an adult aHUS patient, and certainly not one for an adult aHUS dialysis patient. But we agreed to try and were asked to make the case so the hospital could make the request. I remember it took two days of research and draft rewriting to produce a two-page case of why an IFR should be made in my daughter's case. We were not confident after we gave it to the hospital when the hospital staff told us that "no one at the hospital could have made the case as well as we had done", but the application went ahead.

This was all happening concurrently with the "reorganisation" of the NHS which was taking place in 2013 and decision-making committee

structures were changing. The same reorganisation which had forced eculizumab going to NICE for re-evaluation. We waited and waited. Our MP had become involved and was prompting the decision-making group for a decision. Finally, it was approved in May 2013 and with my daughter's waiting time credit given too, the transplant work up which began in 2004 was concluded in June 2013.

It had not been an easy journey.

Very soon after the donor listing confirmation letter, the first call came. Then the second and now the third call.

Would this be the one?

CHAPTER 19 11th December 2013 (part 3)

There was no rush!

Strange how the media portrayal of transplant stories is of a quick action drama, with blue lights flashing, does not seem to be so in the real world.

I finished the NICE meeting. My wife and my daughter went to watch our grandson's school play as previously arranged. My daughter had been to the hospital for the usual pre- transplant check for antibody compatibility etc.

Until the "go ahead decision" it was not thought odd that a prophylactic eculizumab infusion had not been done as per protocol for an aHUS patient transplant.

In the early evening she returned only to be told she could go home to wait and return in the early hours of the following morning. There was going be a transplant.

Our family went to the hospital as requested at 2am and got settled into a room on the transplant ward. Still no eculizumab infusion and we began to mention it to the staff who seemed unconcerned. Then we got the news that she was to be next in theatre and a porter would arrive soon to take her down to theatre.

We were alarmed after all the time spent getting access to the drug, she needed no one seemed to care that she was not to be given it. I spoke to the Sister in charge of the ward and told her that according to protocol she was to receive eculizumab before surgery. With the usual afront to being challenged I was told that they knew what they were doing, they did it all the time. I pointed out that was not the case as this was the first UK cadaver donated kidney transplant supported by eculizumab ever, so this was different.

It made no difference they would not listen. In less than 24 hours I had been relegated from an expert witness being listened to at a NICE meeting about aHUS and eculizumab, to being a numpty over anxious parent who did not know what he was talking about. Yet I was the one who knew what the official clinical protocol was. I was on a committee that established it.

This demonstrates that no matter how detailed and correct a clinical protocol can be decided upon by experts and eminent medical practitioners, it could all be for nothing in practice, let down by the weakest link in the delivery chain. That Sister, that night, was the weakest link. She did not know she was, she was used to the common routine not the rare and innovative. No one had told her. Now she would not listen.

We were just as we were in the first transplant in 1999. “Plus ca change plus c’est la meme chose”

Except there was a new interim aHUS Expert Centre in Newcastle. aHUSUK had designed a patient card with contact details. We got the telephone number from it and asked to be helped. Within a few minutes we had a call back, it was Prof Tim Goodship he was on duty I had only seen him less than 12 hours earlier at the NICE meeting.

We told him what was happening, and he said he would contact the hospital.

Meanwhile the porter arrived, and my wife confronted the health care staff refusing to let our daughter to go to theatre until Prof Goodship had spoken to the hospital.

Time passed and then we heard that her operation had been rescheduled and that the pharmacy had now been asked to supply the drug. After nearly 13 years of waiting it is hard to believe that we would ever put anything in the way of a transplant but that was what we had been forced to do.

The drug came eventually, and infusion begun. It had not finished infusing when another porter came to take her to theatre, so off she went with the saline drip following her trolley.

Now the situation changed as it became what all families facing a transplant feel. Would the operation go well, would the grafted kidney work? The risk in recovery while immunosuppressed and the regime of medicines to take daily (transplant patients in the media never seem to have to face that most dramatic of changes).

That is all aHUSUK had ever wanted for aHUS dialysis patients. Just to get them on a level playing field with other transplant patients. We knew that life with a transplant came with baggage, but it was nothing like the burden of dialysis. Even the two-week eculizumab infusion for life was more endurable than sticking needles in arms five or six times a week to link up to a dialysis machine. It was to be freedom as the Trustee for aHUS Patient Voice, who was now in theatre, had said

But at that time for the reluctant advocate it was just about sitting and waiting for the operation to be over. When all had been said and done that had led to that moment, that other realisation enters transplant patients' thoughts. Someone somewhere had lost their life today and their family were having the worst day of their lives.

They would be remembering those 24 hours for a much different reason today.

11th December 2013 - a bitter sweet day.

Chapter 20 Advocacy Lessons Learned So Far

By Christmas 2013 it was over two years since aHUSUK, and my part in it as a reluctant advocate, had begun. (click here for the story so far)

What had been learned so far from my experience of patient advocacy for aHUS?

- No one wants to be a volunteer but sometimes circumstances thrust it upon you
- If you must advocate, have an important reason, particularly a personal one to do it
- Find like-minded people for the cause as their support is essential, whether in your own country or abroad
- Learn about your subject, not just your own circumstances but also the journey of others'
- Learn skills you do not have, it is sometimes very easy to do so when you must use them
- Understand the processes you must follow, become expert in them and try to keep one stage ahead
- It is not just about emotion, you are in competition with others just as badly off
- Decision makers need evidence, evidence in your favour is king, gather it
- For evidence against what you want, raise reasonable doubt about it if all else fails
- Have simple plans to follow
- Be prepared to change them if something new happens
- Develop your voice and be confident in using it
- Do not be afraid to challenge wisely and take calculated risks
- Develop a core message about what you want and repeat it
- The internet is powerful but use the social media sparingly and keep to the point
- Be patient, try to work smarter and not harder, you have more time than you think

- In their moment, ordinary people can achieve extraordinary feats together
- However sometimes people will let you down, their perception may differ
- And if the “wearing a tutu” is an option offered -TAKE IT! None of the above will apply
- Keep a sense of humour there will be dark times when you think you are losing

Chapter 21 What will their fate be?

The NICE evaluation meeting had taken place in December. aHUS families in England entered January 2014 with the uncertainty of their fate and what NICE would decide and tell us later that month.

Unsurprising as we learned by then we soon found out we would not find out in January as NICE announced the following to participants:

"Dear Consultees and Commentators

Highly Specialised Technology Evaluation

Eculizumab for the treatment of atypical haemolytic Uraemic syndrome (aHUS) [ID703]

Following the Highly Specialised Technology Evaluation Committee meeting on Wednesday 11 December 2013;

• If an Evaluation Consultation Document (ECD) is produced, this will be sent to consultees and commentators in the week commencing 17 February 2014

• If a Final Evaluation Determination (FED) is produced, this will be sent to consultees and commentators in the week commencing 10 March 2014"

The two documents needed some explanation.

1. **Evaluation consultation document (ECD) if produced**
The Evaluation Committee make its provisional recommendations in the ECD. An ECD will be produced only if the recommendations from the Evaluation Committee are restrictive. A restrictive recommendation will be one that is more limited than the instructions for use that accompany the technology. Consultees and commentators have four weeks to comment on the ECD. The ECD is also made available on our website so health professionals and members of the public can comment on it.

2. **Final evaluation determination (FED) produced,**
The Evaluation Committee considers the comments on the ECD if produced, then makes its final recommendations in the FED on how the technology should be used in the NHS in England. Consultees can appeal against the final recommendations in the FED.

So, if an ECD is issued it would not be the end of the matter. If it was to be a FED it would be the end, subject to appeal.

We subsequently heard that any ECD would be released in the week commencing 24 February.

That made us think.

As part of our involvement in NICE aHUSUK had to sign a confidentiality agreement and it prevented us revealing anything in the public domain about what we had been told us for 7 days after we had been told.

The earliest we could say anything to aHUS families about the result of an ECD would be 3 March, 3 days after Rare Disease Day 2014.

The Rare Disease community was wary about NICE is involvement in these decisions. Would a “not re commended” decision not be palatable in the Rare Disease community at a time of heightened awareness

A negative result would not go down well on Rare Disease Day. Better for Government for it to come after. March 10th for a Final Evaluation Decision would mean nothing would be heard by Rare Disease Day.

The wait continued it looked like our fate certainly was that it would not end soon.

CHAPTER 22 Awareness break though?

A large part of patient advocacy is about raising awareness of the illness they suffer. This is particularly true of rare diseases which few people get, and few people know about. After all most aHUS patients had never heard of aHUS until they got it. Many would not even be aware of Rare Diseases.

aHUSUK had done so much to raise the profile of aHUS and had notable results in the political arena as well as the media, TV, Radio, Newspapers and Magazines.

Within in a few days of her transplant in December my daughter had been filmed in our house for a news item about organ donation and the need for families to have a conversation about what they wanted to happen just in case it should happen to them.

Even so it was an enormous surprise when a story line about aHUS featured a long running British Saturday night “soap opera” called "Casualty". Based on a fictional hospital in Holby City (somewhere in Southern England, although the series is filmed in Welsh Studios) each episode has two or three intertwined stories about medical conditions told in a dramatic way.

On 18 January 2014 aHUS was one of the medical conditions to be featured. It was about an ahu’s patient Emily or “Em” as her family called her. This synopsis of the aHUS story line was posted on the aHUSUK website the next day.

aHUS “CAR CRASH” CLIFFHANGER

In Saturday’s episode of BBC’s Casualty, a 21-year-old girl (who we find out had experienced what we know to be the “car crash” of aHUS), became a victim of a “Casualty Car Crash”. The story of Emily, who had been a dialysis patient for 18 months, had begun that day, her 21st birthday, with a hospital appointment at which it was decided that she would receive a new kidney from her sister, Nina.

A limousine then takes Emily, who is very non-compliant with dialysis treatment, and her sister to her birthday party. During the journey, because of an errant popping of a champagne cork the limousine ends up in the predicament shown in the featured photo.

It was while the Doctors were preparing for her rescue and her recovery that it became apparent that Em had a rare genetic disease called atypical Haemolytic Uraemic Syndrome and she was "one in million".

Both sisters are rescued.

They end up side by side in a Casualty Ward in A&E (ER), where concern about Nina's kidney function deepens because one of her kidneys may have been damaged in the crash.

Just as you might be becoming increasingly concerned about an aHUS patient receiving a transplant without a complement inhibitor; the girls' mother reveals that the drug had been approved to enable a transplant to happen.

But then she said after "18 months of hell, tests and diagnosing and waiting the drug supported transplant may not go ahead…….!"

We never heard what happened to Em and her sister, but it was good to know the drug had been approved. Although at that date aHUSUK was not aware!

Chapter 23 Rare Disease Day 2014 Across Borders

aHUSUK support for Rae Diseases had grown each year. By 2014 it had reached a pinnacle for such a small organisation.

We were present for the unveiling of Alexion's "raise your hands " artwork in London. aHUS patients and carers had participated in it.

We attended all the Home Nations' Rare Disease Day events in their parliaments. I attended the one in Northern Ireland although sadly it was not to be held in Stormont, the home of the Northern Ireland Assembly.

Held in Queen's University Belfast, and with the theme "Joining together for Better Care", on Rare Disease Day 28th February 2014, the conference was attended by several hundred rare disease patients and patient organisations from both the North and South of Ireland.

Early in the proceedings the Health Ministers from both administrations gave talks about their respective Rare Disease Implementation Plans.

Edwin Poots, MLA, (see photo above) expressed determination to make things happen but was pragmatic and that it will be a matter of "incrementing progression" over time.

Alex White, TD, outlined some of the Rare Disease infrastructure being put in place, like the National Office for Rare Disease in Dublin. By the time it was opened in June 2015 he had been replaced as Health Minister by Leo Varadkar, and eculizumab had been approved for aHUS the preceding February.

aHUSUK was by Rare Disease Day 2014 aware of a small number of aHUS patients in Northern Ireland as well as several aHUS families in England with familial links with areas in the South West of Ireland.

Before I left my hotel for the conference, I was interviewed live over the telephone by Radio Wales about Rare Disease Day. This led to me talking about my family in a part of Swansea, a city in South Wales. The penetrance of aHUS in my family meant that they dominated the Welsh aHUS patient cohort. aHUS in my family had come from England.

Both Irish Health Ministers saw cross border collaboration as very much needed to make a difference for those with rare diseases.

I could identify with that on Rare Disease Day 2014.

Chapter 24 No one said it would be easy

We had received the Evaluation Consideration Document the week before Rare Disease Day and we participated knowing what we knew but not able to say anything in public. So, patients would not be aware.

NICE were minded not to recommend eculizumab for aHUS. The prime reason was Alexion's inability to explain why the price was what it was.

We could not imagine that a company like Alexion had no clue about why its price was what it was, but we were at a loss to understand why it was unwilling to explain itself. Despite assurances that it would do all it could on price for use of eculizumab for aHUS., it had failed.

The clinical and patient case had been made. Alexion did little different to what it had done at AGNSS. It had not made an offer for a patient access scheme nor was it able to explain its price. An accountant could easily explain it. It is what we said to NICE at the outset.

aHUSUK was as baffled by this outcome as it is convinced that as a patient organisation, it could not have done more to make its case. NICE had told us, as did AGNSS before it, the patient case was made.

aHUSUK was dissatisfied with the way aHUS patients have been treated by our health authorities over the past two years. aHUS patients must have felt devastated at hearing what NICE is now telling them.

We were back to where we were and having to keep that secret for a week built up our frustration and annoyance. We were unhappy with both Alexion and NICE.

I was invited to talk through the decision with the NICE patient engagement team in early March. I said before I left for the meeting that if NICE wanted to say “no” we would be facing a Final Evaluation Document at this point so maybe it was a case of "needing to read between the lines”. At the meeting I think I was forthright and angry as I felt aHUS patients would be about this latest hold up. The explanation I got from NICE was to "read between the lines". I left assuring them we would do all we could do to lobby Alexion to concede what we had implored them to do on price. I also said that we would challenge the figures being used by NICE to question the affordability of aHUS patient treatment.

So, reading between the lines NICE would wish to say "yes" but needed more reasons to justify doing so. Those reasons relied mostly on Alexion.

NICE said there would be another meeting in April after the formal responses to the ECD had been received from all.

So, this was now set to go on and into the Summer.

aHUSUK view on it was “*Drawn out over almost two years, three separate evaluations have been carried out of a drug that everybody admits is clinically wonderful and life transforming. Has any other group of patients ever been put through such an ordeal and had its hopes raised, then dashed, then raised again now dashed again? And all the patients have done is to be unfortunate enough to have a rare genetic condition.*

Fortunately, we had CPAG’s Interim Policy because, without it, what had happened to aHUS patients would have been unbearable. Although it is yet to be confirmed by NHS England, whatever NICE’s final recommendation is to be the

drug will not be withdrawn from those already benefiting from it to save their lives and preserve their kidney function.

The sticking point has existed for 21 months now and aHUSUK had, on several occasions in that time, exhorted both the NHS and Alexion to get around the table to talk, clarify and collaborate on a sustainable solution because simply that is all that is needed. But our exhortations so far had been in vain.

It looks now as though NICE sending aHUS patients back to square one was inevitable, even if unforgivable; but we can only hope that at last, a suitable and sustainable solution can be found. So, it is now up to those, whose job it is to do so, to use the next few weeks to simply get it done."

Enduring all this makes a mockery of those who would claim later that eculizumab for aHUS Patients was got by going through a "loophole" denied to them. Some bloody loophole!

It is not easy being an advocate. It is not irrational to not want to be one. For us it was not as simple as just occasionally putting some sentimental quotes on Facebook. it was now like being in a business environment but not paid. No one said it would be easy.

Chapter 25 A new global direction presents itself

By now followers of the Reluctant Advocate will no doubt have grasped the expansion of work that naturally occurs when running a charity to help people get the best of health. Sometimes this work has a global impact.

Apart from creating awareness about rare diseases, a greater understanding was emerging of the range of issues that rare diseases patients face, from diagnosis to research and registries for their disease.

In April 2014 I attended a second meeting of the Rare Disease Group for aHUS, a part of the Rare Renal initiative of the Renal Association funded by major Kidney Patient Organisations like Kidney Research UK. Although I used the meeting to brief other rare kidney organisations about what had been learned from our experience of NICE, something else caught my eye.

This meeting coincided with the annual UK Kidney Week conference that year held in Glasgow, Scotland. We were given a Conference pack, and, for the first time I realised what was involved in such conferences. That in addition to lectures there were what were known as “poster presentations”, in which hundreds of individuals in an exhibition room put up posters to explain what had been found in some research that they had done.

The pack included a memory stick containing files of the Kidney Week programme and I did a search for anything related to “aHUS” or “eculizumab”. Among several search results I noticed a presentation by Dr Sally Johnson on behalf of something called the “The Academy of Complement Inhibition” about a Global aHUS Registry. The research was

about the characteristics of just over 200 aHUS patients who had been enrolled in the Registry by then.

As Rare Disease Patients frequently face having no patient Registry for their Disease, here was one I knew nothing about for aHUS. So surprised and pleased to find I wrote about it on the aHUS UK website having researched more about it: Probably the first and only patient organisation to do so at that time.

"*This registry sometimes referred to as an Alexion Registry has an official title of* ***An Observational, Non-Interventional, Multi-Center, Multi-National Study of Patients With atypical Hemolytic-Uremic Syndrome (aHUS Registry)*** *and is officially a clinical trial listed by ClinicalTrials.gov. It was established in 2012 and will continue to recruit until 2023 and the outcome will be published in 2025. By that time, it is expected there will be 2000 patients registered. Although sponsored by Alexion the data is being stored by Ohio State University*. Full information can be read about it on ClinicalTrials.gov website by clicking here. The registry is being overseen by a Scientific Advisory Board of International aHUS clinical experts.*

* this was a misinterpretation of the site information where data was being collected as the website entry had not included all the enrolment sites.

And that was that as far as I was concerned. I knew the Registry would be operating until 2025 and so I expected no more than to see updates of what it discovers.

Then in June I got an e mail. It was from someone who was managing the Registry. The Scientific Advisory Board of the

Registry had discussed and agreed at its May meeting that it should have patient input to what it was doing. Orphanet and EURORDIS/ Rare Connect had referred the Registry official to aHUSUK.

After the e mails and a telephone conversation, followed by a face to face meeting, I agreed with the Registry officials that it should be the aHUS alliance (of which they had no knowledge) not just aHUSUK which provides a patient representative; but I could not make that decision. It would have to be agreed by alliance affiliates at their next meeting, planned for November.

At its first meeting in Barcelona the alliance had identified working with international aHUS Research Networks as one of its aspiration. It now had the opportunity to do that. It could provide expert advice for healthcare and research for the benefit of aHUS patients globally.

Chapter 26 Here comes the Sun

aHUSUK formally responded to the ECD decision by 25 March 2014 as requested by NICE. We challenged its decision; but agreed to do what we could to find evidence on affordability and asserted that NICE and Alexion find sustainable solutions on price.

There was no NICE meeting in April as planned. instead consultees were asked to comment on the accuracy of a piece of research that had been done for the NICE committee by some financial consultants. The 60-page report was of a study that had compared 26 (out of 168) highly specialised technologies (drugs appliances and surgery) including eculizumab for PNH (but not aHUS) in the NHS' Specialised Service portfolio.

It adopted a range of 10 or more quantitative performance indicators about severity of illness, impact on health, costs, value for money, innovation cost (R&D), and impact on specialised service delivery and budget to provide a holistic quantitative view of the relative merits of these technologies.

It was realistic about the data barriers that this attempt at comparison faced for all the technologies included in the study. So, for each indicator it assessed the data reliability (scale of 0 to 3) that could be put on it for each of the technologies.

It was remarkable bit of research on rare disease technology evaluation that, as far as is known, has never got into the public domain.

The analysis presented to us was very difficult to understand, really difficult.

But what could be observed was that except for the annual price per patient (based on adult doses at licensed dose levels) of eculizumab, aHUS compared favourably with other illnesses such as PNH and Cystic Fibrosis which had already been approved. Given its clinical effectiveness and exceptional Quality Adjusted Life Years scores, the comparative value of eculizumab for aHUS was looking good to us, and we said as much.

We might not be able to run faster than the lion chasing us, but we could run faster than others it was chasing.

Rare Disease Day had come, and Rare Disease Day had gone. aHUSUK had not sensed that there was much interest or concern by the wider Rare Disease community in the plight of aHUS patients. It would be normal for others to think what was happening would not happen to them and they would do a better job of it anyway. Fair enough.

For all the "better togetherness" of rare diseases in the drive to get equity for patients with such diseases, there was an emerging sense that as far as health care access to cash strapped providers is concerned there was a sense of competition too.

All I knew was that we had not said it was unfair that PNH patients got Eculizumab and we didn’t. I had also signed a petition supporting Cystic Fibrosis patients getting access to a drug they needed.

It was also making me think though, could "single mindedness" result from being a patient advocate, or was it a quality for doing it in the first place?

Back to NICE, we knew that instead of a meeting on the 24th April, aHUSUK had to meet an extended response period by 6 May to give our views on the Report. Soon after that we were informed that NICE were planning for a Final Evaluation Decision in September and for that the next meeting of the Committee would be on 23rd July in Manchester.

I had booked my summer holiday; my flight out was on 23rd July!

Here comes the sun, maybe?

Chapter 28 £2billion a week and counting

By 2014 it was not unusual for aHUSUK to get emails from news journalists from newspapers, radio and TV. It was a big surprise however to get an e mail from a TV production company asking to consider featuring aHUS in a documentary about the NHS.

We met with a producer to find out more before we could say whether we should contribute.

The Producer told us the documentary was being made for one of the UK's main TV channels, Channel 4, and expected to be broadcast in Autumn 2014. The documentary's theme was about the choices facing the NHS in using its £100 per year budget (£2billion per week) It would be a three-part mini-series. aHUS would feature in one of the programmes as representing rare diseases alongside two other more common uses of using NHS resources. (These turned out to be those suffering from drug and/or alcohol abuse, and those who needed better quality prosthetic limbs). The angle for aHUS would be the need for the most expensive drug in the world.

The Producers said it would be done in a novel way in that there would live social media interaction for viewers to give their opinions on what they were seeing and what their preferences were for spending by NHS there may even be a viewers' vote like a reality TV show. Although a bit apprehensive about the interactive facet, the trustees thought that it would raise awareness of rare diseases generally as well as making more people think about aHUS. (it might even result in someone getting an aHUS diagnosis in the future when they may have not)

We also knew that we had a panel of media savvy aHUS patients/ families with good stories to tell.

To get a better idea of the challenge we were facing, see the 40 second trailer to the series click **here**

So with all approvals in place filming begun and by July several patients had been interviewed, one had even had her kidney transplant filmed. Even NICE would allow the documentary makers into its July meeting which I would be attending (although no sound recording of the proceedings was permitted.to be recorded.)

Although I tried not to be included (" I have a face for radio and a voice for newspapers" I told the Chair of the NICE Committee when he ribbed me about being filmed) increasingly the programme makers did begin to focus on our family. It was also clear the filming would continue until the NICE decision was made and its broadcast had been delayed until the New Year.

For that decision to be positive, the 23rd July meeting was now critical.

Chapter 27 Finding Baby Bodmer – learning about aHUS

All aHUS Patients and their families have had their own aHUS experience. When it hit them, most knew nothing of the disease itself but they soon learned about what it did and felt like.

Bit by bit they would begin to understand why it might have hit them . But only “Bit by Bit” over the years; a decade or more ago there were very few sources of information about aHUS. More often than not their clinicians knew little too.

I was the same.

Although my families encounter with aHUS went back decades, I knew little about when in 2011 I attended the first UK aHUS conference hosted by Prof. Tim Goodship in Newcastle upon Tyne. Some of what I learned there stuck.

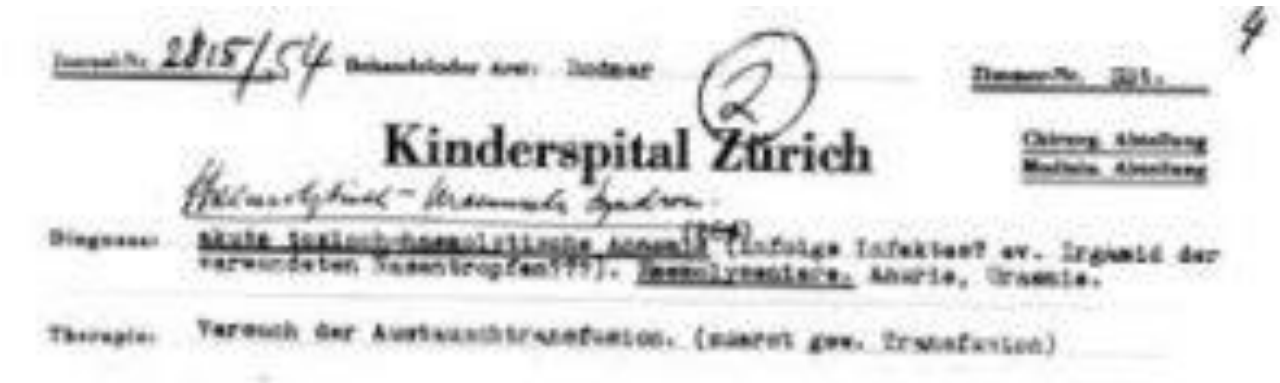
I also watched video recordings of the conference presentations several times to try to understand more. There was a lot of medical jargon to get past, and even when that was got past, the more that was learned the more questions came to mind.

When I was reading all the evidence provided for the evaluation of eculizumab by AGNSS, I was in a privileged position, unique in fact. I learned so much about many facets of aHUS, but also learned “how to understand” some very complex issues. I likened the process to the way 3D images appear from one of those computer-generated confusing patterns.

The more I read the more that certain things jumped out of the page at me. Somethings did not, so I would put those to one side and more often than not they would crop again in another context and their meaning and significance would become apparent

Also, because I was struggling to understand topics, I could empathise with others who were also struggling. Certain topics like “What is a Rare Disease ? “ “What is the difference between the incidence and the prevalence of aHUS ?” , “Why does aHUS not happen to all in families? “ “Why does aHUS have barriers to diagnosis? “ “What precisely is it about Complement that makes it a problem for aHUS patients? I tried to find why they matter to those with aHUS.

As someone who has an interest in history I began to explore the history of the disease, about key discoveries and notable researchers. I began to notice that most articles about aHUS, ten or more years ago, mentioned someone called Von Gasser. I delved into the work of Conrad Von Gasser and found that he , in his hospital in Zurich had coined the term “Haemolytic Ureamic Syndromes” to give a name to the disease he had identified in several children in his hospital.


Kinderspital Zürich

In time I learned more about him from aHUS researchers who knew Conrad. Prof Tim Goodship told me about a book written by Prof Bernard S Kaplan entitled “The Birth of HUS“ . Eventually, I made contact with Bernard and he gave me an electronic copy of his book. Reading that book about Von Gasser I even discovered the name of the first patient to be given “Haemolytic Uraemic Syndrome” as the cause of their death. He had crossed out the baby's original diagnosis, and wrote the three words,which have described our illness ever since, in his own hand writing. When Von Gasser finally published his findings, he said the term covered syndromes, that use of the plural was significant as we now know.

A baby whose surname was **Bodmer**. “Baby Bodmer”, as I called him/her, was the first named HUS patient and was a patient at Zurich Children’s Hospital, 65 years ago this year.

From Prof Kaplan I also learned about Von Gasser’s “Swiss Cow Bell “and he sent me a photograph of it. The bell is now in his safe keeping.

Some years later I got to visit the Children's Hospital in Zurich (Kinderspital Zurich), where Von Gasser had practiced, to visit a Dr Schaulke, the then lead paediatrician / nephrologist

(Von Gasser died in 1982). When I was in the waiting room of the nephrology ward, a cowbell was rung to mark the end of the morning ward round. It was just part of the routine for them, but such a surprise to me, it raised goosebumps.

From 2014 onward I began to write articles on the aHUSUK website about all the topics I had researched and tried to explain them to readers, as I had explained them to myself. I was very cognisant of how I had found them difficult to grasp and understand.

Advocates do need to know much more than their own experience. It makes them more able to advocate about the disease in a rounded way for others and not just about themselves.

So as a lay person, in a unique and privileged position, I was getting to know more and more about aHUS. The key thing I got to know about aHUS is that there is far too much to be able to know all. That does not stop anyone asking questions about what matters and seeking more answers to them. In time it would be surprising what we can learn.

On Rare Disease Day 2019 the alliance will be formally launching the "Global aHUS Patients' Research Agenda". A list of research questions about aHUS by aHUS patients. Together we can get more answers.

You are not alone We can find a way