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.

Wimpole Street is a 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 patient 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 “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.