A Parent’s Perspective of the Clinical Trial Process by Susan Green

Thank you for inviting me to talk about a parent’s perspective. Here is a photo of my children taken nearly 30 years ago. Roy is 4, Murray 3 and Ailsa barely 2.

Here they are again three healthy children— or so we thought. Little did we know that we were shortly to begin our journey with Niemann Pick Disease.
Murray was diagnosed with NPC at the age of 12. A few months later we were told that Roy also had NPC. Most people in this room will understand only too well how we felt. Eventually we made contact with some more families and started a support group- the beginning of the NPDG (UK). In listening to families it was obvious that they were all seeing different doctors and no one seemed to know much about Niemann-Pick disease! What we needed was one doctor who could see more than one family and learn more about this disease. Fortunately I was invited by Dr Sardarwaller to visit the Willink Biochemical Genetics Unit in Manchester “to see how they might be able to help”. Dr Sardarwaller had recently retired as Director of the Willink and was keen to introduce me to the new Director, Dr Ed Wraith. Dr Wraith offered to hold a clinic for patients with Niemann-Pick Disease - the rest is history!

Shortly after the boys were diagnosed, I had also written letters to everybody I could think of who might know about this disease (no internet or email in those days!). Eventually I received a letter from the National Institutes of health in Bethesda, USA. They said that they were conducting a clinical trial on the use of cholesterol lowering drugs for NPC and wondered if we would like to be involved!
Murray’s seizures were proving difficult to control and he was too ill at the time, so..

Roy and I went by ourselves. We were made very welcome and met Dr Roscoe Brady who was in charge; Dr Peter Pentchev, the biochemist, and a young Australian doctor who was working there called Dr Marc Patterson. We also met some parents from the US who had taken part in the first part of the trial, to see if the drugs could reduce the amount of cholesterol in the liver. The second part was to see if the drugs had any effect on the brain. Unfortunately there was a problem with funding for the next stage of the trial. Some of the families who had been on the trial had arranged a meeting with the doctors involved to see how they might raise funds to help with the research. Roy and I were invited to come along to what would turn out to be the first meeting of the National Niemann-Pick Disease Foundation. The folks at NIH said that they would be pleased to enrol both Roy and Murray on the trial when it got going again.
Jim and I knew that, if we wanted the boys to be part of the trial then we would need money to get us there on a regular basis. We went public with our story in the local Newspaper. Not an easy thing to do! Our community in Hawick were fantastic and rallied round to help. In this photo I am clutching our tickets to Washington! Unfortunately the second part of the trial did not take place. The clinical endpoint was to have been walking ability, which was the only thing they could measure. This meant that it would have needed to be a double-blind multi-centre trial with 100 patients, over two years. There was not enough funding. This was very disappointing. However they did want to see patients, including Roy and Murray on an annual basis to monitor the course of the disease. Later we heard that they were close to identifying the gene for NPC but needed blood samples from families with two or more children. We all gave our blood and we sent letters to all of the families we knew in the UK with two or more children, giving instructions on how the blood should be collected and shipped to the NIH. They all sent their blood!
The difficulties with not having a suitable marker that could use to measure whether a therapy was working, led to another small clinical study involving just three young adult patients. This was conducted by Dr Chuck Schwartz in Richmond Virginia. Roy agreed to take part.

It involved having a tube inserted through his nose into the upper bowel to collect bile every two hours and two-hourly blood tests. The aim was to measure the size of the cholesterol pool in the body. The only difficult part for Roy was that he was not allowed anything to eat all day!
At the end the nurses presented him with a chocolate cake! They had heard that it was his birthday next day. Roy was delighted!

It was good to be home again but we were realising that time was running out for Murray
In October 1996 Murray, our wonderful, funny, amazing son died. He was 18 years old. No amount of research could help Murray now.

Our journey with Niemann-Pick Disease continued, there were many challenges to come.
In June 1997 Dr Gene Carstea came to our conference with the exciting news that the NPC1 gene had been found on chromosome 18! There was celebration all round. We all felt that a treatment was just around the corner!

Roy continued to attend NIH every year and enjoyed meeting every one again while they collected samples, and information. His particular favourite was Jackie; she let him go to sleep when he was having his EEG!
Roy also enjoyed the food!

We were always made to feel welcome and people went out of their way to answer all of our questions. We even spent some time in the labs learning about the research. Roy is busy looking at his cells through the microscope.
Roy and I usually managed to time our visits to NIH with attendance at the NNPDF family conferences. Roy would sit in on most of the presentations and was often found in conversation with researchers. Here he is with Dr Steve Sturley 'the yeast man'.

All this galavanting around can be tiring! Meanwhile the clinical research was moving ahead in the UK. We had the largest group of Niemann-Pick patients being seen regularly by one doctor in the world! We had a clinical nurse specialist supporting patients and gathering information. We had the first clinical trial starting for miglustat, or OGT 918 as it was known then. It was exciting! It was Dr Fran Platt that I first heard talking about sugar A, at a Climb conference. Its real name n-butyldideoxynojirimycin was a bit too long! Then Dr Steve Walkley also gave a presentation on his work with N-BDNJ at an NNPDF conference. I asked him if he had met Fran and he said no, he had only read her research papers. So we invited them both to the next NPDG(UK) family conference. Theirs proved to be a very productive partnership.
Roy was one of the first patients to be screened for enrolment in the miglustat trial. Here he is on the way to Manchester for the first screening visit. It was very exciting to be involved in something for which we had waited so long.

On the second screening visit he met the speech therapists who did the swallowing assessment.
He enjoyed that bit because he got to eat again!
Then there was the nerve conduction test – he definitely didn’t like that!

Next, the nutritionist, Roy always likes to talk about food!
We then went to Sheffield by taxi to do the eye movement test. Disaster! Roy couldn’t do it. He just kept falling asleep. It meant that he would not be able to be on the trial. Everyone was devastated! except Roy who just wanted to sleep. There were even some tears and I found myself comforting them. I was horrified, if Roy couldn’t do the test, how would the little ones manage? This could screw up all of the study! People kept apologising that Roy would not be able to take part and all I could say was, “that’s OK, the important thing is that the trial goes ahead”. The journey home was awful. I desperately wanted to talk to Jim but I couldn’t because Roy was there. I didn’t want to upset him although he seemed to have forgotten all about it – dementia can be a blessing at times! We were all bitterly disappointed but resigned to the fact that Roy would not participate.

We went to NIH as usual in the summer and Dr Fitzgibbons, the ophthalmologist who Roy saw every year, asked how he was managing with the trial. When I explained that Roy was not on the trial
because he could not do the eye movement test Dr Fitzgibbons said, “That’s nonsense, of course he can do it, that’s what we do ever year”! He made a phone call and it was agreed that Roy could do the test again with Dr Fitzgibbons who was the person doing the test for all the USA trial patients. Roy passed with flying colours!

Back to the Willink in November and Roy was finally enrolled on the trial. He was very pleased – I was stunned!

Helena and Jackie were delighted! The worst part was over, it was all uphill from there. That is except for the diarrhoea... but that’s another story. I now know what the phrase ‘when the shit hits the wall’ actually means. Seriously, we have been very well looked after at every stage of the trial.
We were delighted that some of the symptoms actually improved at the beginning, especially Roy’s speech and swallowing. That was an unexpected bonus. There are no miracles however, the disease continues, but slowly. Being on Zavesca we feel has helped to maintain Roy’s quality of life for much longer than we expected. The fact that he is still able to eat heartily has helped a great deal to keep him in good health. As Roy used to say, “If it wasn’t for the Niemann-Pick I would be fine”!

Roy is now 33 years old and still manages to enjoy himself and get a good catch of fish!

His journey with this disease continues. Roy was always keen to be involved in research. He felt it was important. He would say, “If he doctors are trying to find some answers to this disease then we need to do our bit to help”. Roy is no longer able to travel to NIH but we were asked last week if Roy
would be willing to be part of the extension study for the N-acetyl cysteine trial at NIH. They need more information on adults with NPC and would like to access Roy’s medical records. I asked Roy and he replied as he always has in the past, “Go for it”!

When the NPC1 gene was found Dr Peter Pentchev said, “The identification of the NPC1 gene is the fruit of a successful partnership between scientists and families and is a significant step in the research of Niemann-Pick disease type C. Scientists from many countries worldwide contributed to these findings by sharing data and cell lines from affected families. The Niemann-Pick Disease Group (UK) helped by locating families with children affected by the disorder and the investigators received major financial support for this work from both the APMRF and the NNPDF. He said that families with children affected by NPC have been important for much more. When he first began studying the causes of this disease, the lack of knowledge led to an ‘incurably hopeless wasteland’. Even worse, the disease was one of the ‘orphan diseases’ that strike only a small number of people, leaving drug companies and most laboratories little incentive to understand them. The parents did not accept this hopelessness, he said, they took it on their own shoulders to enquire about what causes this disease. We had NOTHING but their courage. These pioneering families, their faith and perseverance, that’s what led to the cloning of the gene”.

We have come a long way since then. We now have an approved therapy for NPC, and more clinical studies and trials taking place. Dr Ed Wraith and his team in Manchester are at the cutting edge of clinical research. As well as Dr Wraith, we have a clinical research nurse as well as a clinical nurse specialist, publishing research papers based on clinical observation of a very large group of patients. We have a team of dedicated clinicians and scientists in the field of Niemann-Pick Disease and new people being drawn into this field. Hundreds of research papers now appear on pub med. We have
two top quality pharmaceutical companies committed to developing therapies for NPD as well as International Registries of patients. Recently, a coming together of Niemann-Pick support groups worldwide led to the formation of the International Niemann-Pick Disease Alliance. All of this and more based on ‘the commitment of pioneering families, their faith and perseverance’

If you ever feel that you would like to take part in a clinical trial then, as Roy would say GO FOR IT!

Thank you for listening.